Mild traumatic brain injury : intervention and prognosis

MILD TRAUMATIC BRAIN INJURY INTERVENTION AND PROGNOSIS

Universitaire Pers Maastricht
ISBN 90 5278 332 2

The publication of this thesis was financially supported by
GlaxoSmithKline, Merck Sharp & Dohme BV, Janssen Cilag BV, Serono Benelux BV, Baxter BV, Novartis Pharma BV, ASTA Medica BV, Sanofi Synthelabo and Schering Nederland BV.

Vormgeving en druk
Datawyse | Universitaire Pers Maastricht

Cover illustration
Gerda Dendooven
In: Toon Tellegen, *Dokter Deter*, Amsterdam, Querido, 1997

MILD TRAUMATIC BRAIN INJURY INTERVENTION AND PROGNOSIS

Proefschrift

ter verkrijging van de graad van doctor
aan de Universtiteit Maastricht,
op gezag van de Rector Magnificus,
Prof. dr. A.C. Nieuwenhuijzen Kruseman
volgens het besluit van het Collega van Decanen,
in het openbaar te verdedigen op
donderdag 20 december 2001 om 16.00 uur

door

Jelle de Kruijk

UNIVERSITAIRE PERS MAASTRICHT

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The research presented in this thesis was performed at the department of Neurology of the University Hospital Maastricht.

Dokter Deter maakte veel mensen met hersenschuddingen beter. Als ze op zijn stoep lagen te kreunen tilde zijn knecht ze op en droeg ze naar binnen.
Er was een speciale kamer voor hersenschuddingen en hoofdpijn. Dokter Deter had een apparaat om hersenschuddingen los te schudden. Dat gebeurde in het donker, in die kamer. De knecht hield het hoofd vast, dokter Deter zette het apparaat aan en even later was de hersenschudding los en schoot naar buiten. In de kelder stond een kast waarin alle oude hersenschuddingen lagen. Het waren er duizenden. Dokter Deter wist niet goed wat hij met ze moest doen. Maar hij vond het ook zonde om ze weg te gooien.....

Uit: Toon Tellegen, *Dokter Deter*, Amsterdam, Querido, 1997

Voor Annick

CONTENTS

LIST OF ABBREVIATIONS

EFNS	European Federation of Neurological Societies
FULL	6 days bed rest
GCS	Glasgow coma scale score
LOC	Loss of consciousness
MTBI	Mild traumatic brain injury
NSE	Neuron Specific Enolase
NO	No bed rest
PTA	Post-traumatic amnesia
PTC	Post-traumatic complaints
THBI	Traumatic head and/or brain injury
TIAD	Traumatically induced axonal damage
VAS	Visual analogue scale

GENERAL INTRODUCTION

Traumatic brain injury is an important cause of morbidity and mortality and is clinically classified as severe, moderate or mild using the admission Glasgow Coma Scale (GCS) score. Precise incidence rates are hard to obtain, but it is clear that most injuries are classified as mild traumatic brain injury (MTBI). Various criteria have been used for the diagnosis and nomenclature. The usual diagnostic criterion for MTBI has been a GCS score of 13 to 15.(1) Names like Commotio Cerebri, Concussion or Mild Head Injury have also been used. On the basis of more recent studies evaluating the association of GCS scores with the presence of intra-cerebral contusions on CT-scans and with long-term outcome, however, it has been suggested to limit MTBI to cases with GCS score of 15 (= optimal) at presentation.(2-4). Duration of post-traumatic amnesia and loss of consciousness at presentation have also been proposed as additional criteria for MTBI.(2, 5)
Outcome after MTBI is mainly determined by the severity of late post-traumatic complaints (PTC) like headache, dizziness, poor concentration and depression. The severity of PTC declines during the first three months, but their prevalence is still estimated at 20 to 80% six months after the trauma.(2, 6-8) This huge variation probably reflects the different definitions of MTBI and PTC used in these various studies. Most studies have evaluated PTC and/or neuro-psychological test results. Although information about impairment of daily life activities would also be helpful in assessing the consequences of MTBI, only a few studies have measured generic health status in MTBI patients.(9, 10)
Within hours after the trauma, MTBI patients often complain about headache, neck pain, nausea, dizziness and vomiting. Presumably, these early symptoms are caused by the same injury mechanisms as those responsible for late PTC. To date, before 1990, hardly anything was known about the location and pathophysiology of brain damage after MTBI. Since then, research on animal models and post-mortem studies have revealed traumatically induced axonal damage following MTBI, which was mainly located in the frontal and temporal lobes.(11-13) Clinical MRI studies have recently reported signs of brain damage after MTBI, (14-16) while increased concentrations of biochemical markers (S-100B and NSE) suggesting traumatically induced axonal damage have been found in small groups of MTBI patients.(17, 18)
In addition to radiological and biochemical signs, olfactory dysfunction also seems to be related to traumatic brain damage.(19) Traumata particularly associated with olfactory dysfunction include skull-base fractures and occipital blows

(with frontal impact) to the head.(20, 21) Confirmation of olfactory dysfunction after MTBI would support the hypothesis that a mild trauma can damage structures of the brain somewhere in, or between, olfactory nerve filaments and fronto-temporal cortical structures.

Biochemical markers, olfactory function and acute clinical symptoms could thus be useful parameters to asses the severity of brain damage and presumably improve the prediction of PTC after MTBI. Associations between such acute MTBI parameters and outcome have not been studied so far.

Prevention of PTC is important because they lead to high healthcare costs and loss of labour productivity.(22, 23) Measures commonly prescribed following traumatic brain injury are rest and / or taking some time off work, but their effectiveness in preventing PTC has hardly been studied.

The value of bed rest was emphasised in the 19th century as the primary treatment of many disorders. A recent review of randomised trials on bed rest for several medical conditions (not including traumatic brain injury) concluded that bed rest did not improve the prognosis, and even worsened the outcome in some situations.(24) As far as we know, only one study has evaluated bed rest after MTBI.(25) The author concluded that bed rest of more than two weeks appeared to be related to more PTC. Notwithstanding the lack of evidence for the efficacy of bed rest, almost half of the neurologists in the Netherlands recommend one or more days of full bed rest after MTBI.(26)

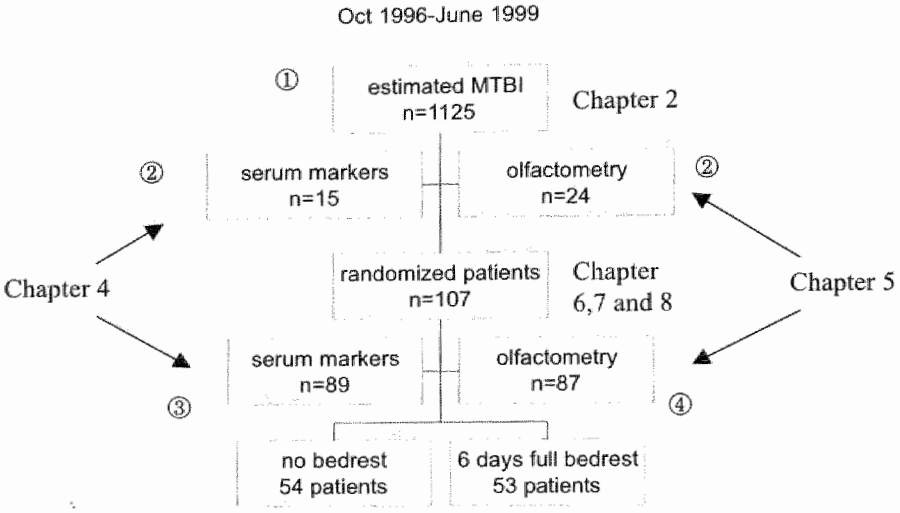
Educating patients at the outpatient clinic about PTC within three weeks after MTBI has proved to reduce the severity of these complaints in the long run.(27-29) Since many MTBI patients do not develop PTC at all, reducing needless follow-up will save money and prevent medicalisation of mainly young and healthy people. Therefore, early recognition of patients not at risk of developing PTC would be useful.

Because of the lack of scientific evidence on the effectiveness of treatment and follow-up of MTBI patients, no guidelines have so far been agreed upon. The aim of present thesis is to provide an impetus to the development of evidence-based management of MTBI patients.

OUTLINE OF THE STUDY

The main aim of the present study was to identify ways of predicting and preventing post-traumatic complaints after mild traumatic brain injury. Before we started collecting the data, literature was reviewed about the definition, differential diagnosis, diagnostic tools and treatment of MTBI (**chapter 1**).Accordingly this overview, we decided upon a useful definition of MTBI and selected relevant outcome parameters for the following studies.
The first two studies estimated the incidence of traumatic head and brain injury in a well-defined catchment area in the Netherlands (**chapter 2**) and surveyed the management of MTBI patients in several European hospitals (**chapter 3**).
The study reported on in **chapter 4** assessed serum concentrations of the biochemical markers Neuron-Specific Enolase (NSE) and S100-B in MTBI patients and in healthy controls. **chapter 5** describes the prevalence and severity of olfactory dysfunction after MTBI and correlates olfactory function or dysfunction with biochemical marker concentrations and the presence of acute symptoms. **chapter 6** identifies clinical parameters (symptoms and biochemical markers) in MTBI patients at presentation that are predictive of the severity of PTC after six months. In order to develop a clinically useful test to determine which MTBI patients do not require follow-up at the outpatient clinic, we also tried to determine a combination of variables that can predict favourable outcome after six months.
The study reported on in **chapter 7** aimed to investigate the generic health status of MTBI patients in the course of six months after the trauma, and searched for associations between the presence of PTC and generic health status after six months.
Finally, in **chapter 8** a randomised trial on the effects of six days of bed rest versus no bed rest on the severity of PTC and generic health status after six months was conducted.

Included patients in different sub-studies



① Number of patients is an estimation for the period between Oct 96 and Jun 99, derived from the described MTBI incidence in chapter 2

② These patients gave consent for follow-up but did not fullfill the trial criteria because they were shortly observed clinically

③ Trial-patients who gave consent to taking blood samples

④ Because of logistic reasons olfactometry was only done by the first 87 patients in the trial

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CHAPTER 1

DIAGNOSTIC CRITERIA AND DIFFERENTIAL DIAGNOSIS OF MILD TRAUMATIC BRAIN INJURY

Presented at the III meeting of the European Federation of Neurological Societies; September 19-25, 1998; Seville

Adapted from:
Kruijk de J., Leffers P and Twijnstra A.
Diagnostic criteria and differential diagnosis of mild traumatic brain injury. *Brain Inj 2001*;15(2):99-107.

ABSTRACT

Brain injury is classified clinically as severe, moderate or mild by injury characteristics, including admission Glasgow coma score, duration of unconsciousness and post-traumatic amnesia and any focal neurological findings. Most traumatic brain injuries are classified as mild traumatic brain injury (MTBI). Headache, nausea and dizziness are frequent symptoms after MTBI and may continue for weeks to months after the trauma. MTBI may also be complicated by intracranial injuries.

Experimental animal models and post-mortem studies have shown axonal damage and dysfunction in MTBI. This damage is mostly localised in the frontal lobes. Serum S-100 and NSE have been reported to be markers for the severity of brain damage.

In the literature, indications for radiodiagnostic evaluation following MTBI have been the subject of debate. Radiographs of the skull are used to exclude skull fractures, but are not useful for an evaluation of brain injury. Computed tomography of the brain seems to be the best way to exclude the development of relevant intracranial lesions.

MTBI has a good clinical outcome, though a substantial group of patients develop post-traumatic complaints (PTC). There is little information on the effectiveness of various methods suggested for reducing the frequency of PTC.

DEFINITION AND CLASSIFICATION OF MILD TRAUMATIC BRAIN INJURY

Historically, studies on features, frequency and management of traumatic brain injury are difficult to compare because traumatic brain injury and head injury have often been used synonymously. Both are the result of contact or acceleration-deceleration trauma of the head. However, only traumatic brain injury is associated with loss of consciousness (LOC), post-traumatic amnesia (PTA) and/or focal neurological signs. The present overview focuses on mild traumatic brain injury (MTBI).

In the literature, traumatic brain injury is commonly classified as mild, moderate or severe, based on the Glasgow Coma Score (GCS) at first examination.(1) MTBI was initially diagnosed if GCS was 13-15,(2) and is also called Commotio Cerebri, Concussion or even Mild Head Injury in some European countries.(3, 4) In view of the extent of neurobehavioural consequences and the possible presence of brain lesions on an acute CT, other authors have suggested that traumatic brain injury with GCS 13 or 14 should be classified as moderate.(1, 5-7) This would imply that traumatic brain injury could only be classified as mild if GCS at presentation is 15. In recent years, duration of PTA and LOC at presentation have been suggested as additional criteria for MTBI *(table 1)*.

Table 1. Criteria for mild traumatic brain injury.

Authors	Criteria
Rimel 1982	GCS 13-15
Williams 1990	GCS 13-15 without brain lesion on CT; Otherwise moderate or severe BI
Vollmer 1991	PTA < 5 min = very mild PTA < 1 hr = mild
Alexander 1995	If LOC: sec-min GCS 13-15 (probably only 15) PTA < 24 hours; (mostly minutes to a few hours) No focal signs No radiological abnormalities
Culotta 1996 and Gomez 1996	Segregation of patients with GCS 15 from those with scores of 14 and 13, based on incidence of necessary surgical interventions

GCS = Glasgow Coma Scale score.
PTA = Post-traumatic Amnesia.

DIFFERENTIAL DIAGNOSIS OF MTBI

Shortly after the trauma, MTBI patients show typical signs and symptoms like headache, neck pain, nausea, dizziness, vomiting and amnesia. It is believed that these signs and symptoms are precipitated by a mixture of brain injury, peripheral vestibular injury and injury to the soft and bony tissues of the head or even neck. Labyrinthal contusion in particular can cause extreme dizziness, vomiting and nystagmus. Acute post-traumatic epilepsy is only reported in about 4% of MTBI patients.(8)

MTBI can also be accompanied by facial and skull fractures. Facial fractures tend to be extremely painful but do not demand acute surgical intervention. It is estimated that between 3% and 13% of MTBI patients have skull fractures.(7-9) The prevalence seems to be dependent on the number of skull radiographs performed in the patient group under investigation. The presence of a skull fracture in MTBI implies an increased risk of intracranial injuries.(8-10)

MTBI can be complicated by intracranial injuries like contusions, subdural, epidural and subarachnoidal haematomas. Estimates of the prevalence of these lesions in MTBI patients range from 5% to 12%.(11-13) Most intracranial injuries are contusions, which do not demand surgical intervention. Contusions are of prognostic value however, because they are associated with a high incidence of post-traumatic sequelae. Intracranial haematomas, especially epidural haematomas may require surgical treatment.

Within the MTBI group, indicators for a high risk of traumatic intracranial injuries include: GCS < 15, focal neurological findings, signs of skull base or depressed fracture, early post-traumatic epilepsy, persistent vomiting, progressive headache and 'High velocity' or unknown cause of trauma.(14)

PATHOPHYSIOLOGICAL ASPECTS OF MTBI

For a long time it was not clear whether MTBI was accompanied by brain damage. Investigations in recent years have revealed information about the location and mechanisms of such brain damage.

EEG power spectra analysis and auditory brain stem-evoked potentials recordings after MTBI suggest that damage to the brain is localised in the cortex and in

the brain stem.(15) Immunostaining techniques have shown multifocal axonal injury in the fornices of the major hippocampal projection pathways.(16) Recently, MRI studies showed cortical lesions in the first month after MTBI. These lesions were predominantly localised in the frontal lobes.(17)
Experimental animal models and post-mortem studies have showed traumatically induced axonal damage following brain injury.(16, 18, 19) Initially, it was believed that tensile forces during the trauma immediately tore axons. Povlishock suggested however that the injury is rather the result of impaired axoplasmic transport, axonal swelling and disconnection over a 3-6 hour period after the injury. This is believed to be the mechanism in traumatic brain injury of all severity's, but the cascade following mild injury differs from that in more severe injury. The endpoint of the cascade in mild injury involves no overt axolemmal perturbation, while more severe brain injury results in altered axolemmal permeability. Both, however, ultimately lead to dysfunction 12-24 hours after injury.(20)
Biochemical markers confirming axonal damage in MTBI are under investigation. Serum S-100B and Neuron Specific Enolase (NSE) concentrations peak within 6 hours after traumatic brain injury and peak concentrations seem to reflect the severity of the mechanical disruption of brain tissue.(21-25) Recently, elevated S-100B and NSE concentrations have been reported in patients with MTBI.(21, 26) However, the patient series were small and no comparison was made with a control group without brain injury.

DIAGNOSTICS IN MTBI

The presence of a skull fracture in MTBI means a 5 times higher risk of intracranial injuries although most patients with intracranial lesions have no skull fracture.(26) Vollmer concluded that information from skull radiographs altered patient management in less than 1% of traumatic brain injury patients.(27) Several authors have tried to formulate clear indications for performing skull radiographs following head injury, but at this moment no international consensus is available *(table 2A)*. Recently, most authors have agreed that skull radiographs are not clinically useful because they do not exclude intracranial lesions.(9, 12, 27) Never-

Table 2A. Indication for skull radiographs in patients with traumatic brain injury.

Authors		Indication		
		PTA	GCS	Other
Masters 1987	If [a]:	+	< 15	Clinical Riskfactors[b]
Vollmer 1991	If:			CT indicated (2B) but not available
Servadei 1995	If [a]:	+	14 or 15	
Gomez 1996	If:	+		
Ingebrigtsen 1997	Never			
Murshid 1998	Never			

[a] = if one or more criteria present.
[b] = Risk factors: GCS < 15,focal neurological findings signs of skull base or depressed fracture; early post-traumatic epilepsy; persistent vomiting and or progressive headache and High energetic or unknown cause of trauma.

Table 2B. Indication for CT of the brain in patients with traumatic brain injury.

Authors	Indication[a]		
	PTA	GCS	Other
Vollmer 1991		< 15	- Focal findings - Open skull-fracture
Servadei 1995		< 14	- fracture on X-skull
Gomez 1996		< 15	
Ingebrigtsen 1997	+		
Murshid 1998		< 15	- Focal findings - Depressed fracture - Persistant headache or vomiting

[a] = if one or more criteria present.

theless, skull radiographs are still frequently performed for brain injury patients in European emergency rooms.(28)
CT of the brain is conclusive but expensive and not always available.
Suggested indications for performing a CT of the brain following head injury are listed in *table 2B*. Performing an early CT of the brain in all MTBI patients seems

to be the best way to exclude the development of intracranial lesions.(12) Small cortical contusions have been found on MRI following MTBI.(17, 29-32) SPECT can show local hyper and hypoperfusion in the same areas.(32-36) The clinical relevance of these two abnormalities is not clear. Abnormalities on MRI and SPECT may be useful for the prognosis in MTBI.(17, 37-40)
To monitor the severity of brain damage, several biological markers are under investigation. NSE and S-100B in serum have been reported to be useful markers for CNS damage after traumatic brain injury.(12, 22, 41, 42) Serum S-100B in particular seems to be promising as a tool for quantifying brain damage after MTBI.(12)

MANAGEMENT FOLLOWING MTBI

Over the past years, the annual numbers of patients with traumatic brain injury admitted to hospitals in the US declined from 199 to 98 per 100.000.(43) Admission following MTBI declined most, from 130 to 51 hospitalisations per 100.000 per year. In 1996, the ratio of patients with mild, moderate and severe traumatic brain injury admitted to the hospital alive was estimated between 8 to 1 to 1.(44) Thurman observed a relative decrease of MTBI hospitalisation rates in the US during the last years.(43) European admission rates for MTBI remain unclear.
Clinical observation seems useful in patients with risk factors for traumatic intracranial complications *(table 2A)*. Difficulties in clinical assessment because of alcohol, drugs or age and lack of a responsible carer are also reasons to admit a patient for observation. It is believed that proper application of such guidelines can further reduce admission rates.(10, 45)
Patients with MTBI discharged from the emergency department should receive instructions for further management. To detect intracranial complications in the first 24 hours following the injury 'home observation instructions' should be given to a responsible person accompanying the patient. However, compliance with these instructions is probably low.(46-48)
Recently, the Oxford Head Injury Service developed an intervention protocol for head injury patients in which reduction of anxiety is the most significant element.(49) This protocol was developed on the recognition that emotional factors play an important role in recovery from MTBI. For patients who experi-

ence post-concussional complaints (PTC), the protocol includes recommendations regarding performance of daily activities, including going back to work. The Oxford Head Injury Service protocol does not include any recommendations to prevent PTC.

Twenty to 80% of patients with MTBI develop PTC within the first 6 months after the trauma.(50-52) Literature reports on the effect of bed rest and 'taking some time off work' on the development of PTC have been sparse. If there is any effect of bed rest and taking time off work at all, its most effective duration is unknown. Bed rest of more than two weeks following MTBI seems to worsen the outcome after one year.(53) Minderhoud found that a 'strict regime' in MTBI patients, including information about possible complications, reduced the occurrence of PTC.(54) Wade found that routine follow-up after head injury reduced the 'social morbidity' and severity of PTC.(55) Some investigators have also evaluated the effect of specific drugs (CDP-Choline and DGAVP) on PTC.(56, 57) No preventive effect could be substantiated.

Presently, no consensus exists among European hospitals regarding the recommendations given to patients with MTBI who are discharged from the emergency room.(28)

CONCLUSIONS

There have been many studies of MTBI. However, these studies are characterised by lack of uniformity in the diagnostic criteria applied. Future studies in clearly defined MTBI should aim at the elucidation of the effectiveness of various aspects of management in MTBI patients. Results of such studies can be helpful in the process of developing a European consensus.

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CHAPTER 2

INCIDENCE OF TRAUMATIC HEAD OR BRAIN INJURY IN THE CATCHMENT AREA OF THE UNIVERSITY HOSPITAL MAASTRICHT IN 1997

Adapted from:
Meerhoff S, Kruijk de J, Rutten J, Leffers P, Twijnstra A. De incidentie van traumatisch schedel- of hersenletsel in het adherentiegebied van het Academisch Ziekenhuis Maastricht in 1997. *Nederlands Tijdschrift voor Geneeskunde 2000*;144(40):915-23.

ABSTRACT

Introduction: Reliable epidemiological figures about traumatic head and brain injury (THBI) are hard to obtain. This is partly due to the fact that many specialties are involved in THBI care, and partly to the variations between hospitals in the frequency and spectrum of severity of head injury. A frequently used method for calculating the incidence rate of THBI is counting admissions. This could, however, lead to inaccurate estimates because the catchment area is usually not precisely known. The objective of the present study was to measure the incidence of THBI in a well-defined catchment area.

Methods: At the University Hospital of Maastricht (azM), we collected data on head-injury patients who visited the emergency room in 1997. The database was further completed by adding case reports of patients found in hospital records (ICD codes) and records of the Radiology department. The azM is the only hospital in the city of Maastricht and its surrounding area and has an adherent population of approximately 231,000 people.

Results: The emergency room was attended by 1933 THBI patients in 1997. Head trauma without loss of consciousness (LOC) and / or amnesia was diagnosed in 75% (1440) of cases. Mild traumatic brain injury (MTBI) was diagnosed in 24% (467) of all THBI patients. MTBI was diagnosed in 95% of patients with brain injury; de rest was diagnosed as moderate or severe traumatic brain injury (26 patients; 1% of all THBI). The mean age was 30 years (range 0-97) and one-third (29%) of the patients were below the age of 15. Two-thirds (67%) of the patients were male. An X-ray of the skull was made in 15% of the cases. Relevant abnormalities were found in 8% of these X-rays. Eleven percent of the patients were admitted for observation. The incidence rate of THBI in 1997 was 836/100,000 and the incidence of admission 88/100,000. The incidence of MTBI was 202/100,000. The causes of THBI were falls (43%), traffic accidents (22%), violence (15%), sports injuries (7%) and accidents at work (4%).

Conclusion: The proportion of THBI patients with mild injuries (99%, only head injury plus mild THBI) was high compared to that in other studies. The frequency of hospital admissions was extremely low. The fact that this study was conducted in a well-defined catchment area supports the credibility of the data. There were, however, two sources of bias, with opposite effects on the incidence estimate. Problems of identifying patients by case records may have led to underestimation, while inclusion of patients from outside the catchment area may have led to overestimation. Although the precise impact of the resulting bias is unknown, it is believed that the incidence figures from the present study are more reliable than previously published data.

INTRODUCTION

In Western countries, traumatic injury is an important cause of morbidity and mortality. It is in fact the most important cause of death below the age of 45 years.(1) One-third of admissions for traumatic injury concerns head and brain injury.(2) Traumatic head and brain injury (THBI) especially affects men between the ages of 15 and 30.(3) These injuries not only lead to high costs of health care, but also to loss of productivity.(4-7)

More information on the burden imposed by these injuries on the health care system and the social and economic consequences can only be obtained from epidemiological data on THBI. Although several research projects reported in the medical literature have described the frequency of this injury, they have used different names, definitions and registration policies, making it difficult to compare THBI frequencies in a specific area with those in other countries or regions. One of the reasons is the involvement of several specialties in the care of these patients. In addition, there is a group of patients who are seen only by the general practitioner or do not seek any medical assistance at all.(6) Calculating the incidence and admission rates for a country as a whole is difficult because catchment areas are difficult to define. In the southern part of the Dutch province of Limburg, the situation is quite unique in that the specific catchment areas of the various hospitals can be accurately defined. The purpose of the present study was

to assess the incidence of THBI in the catchment area of the University Hospital of Maastricht (azM), measured as the numbers of patients seen in the emergency room.

METHODS

All patients with THBI seen in the emergency room of the azM between January 1st and December 31st, 1997 were included in the research population. Patients who were first seen in the emergency room of another hospital and were subsequently referred to the azM because of its regional trauma center function were excluded.

THBI was defined as the presence of clinical signs of injury to the head or brain. A distinction was made between patients with and those without brain injury. The severity of traumatic brain injury was classified by means of the 'Glasgow Coma Scale' score (GCS; *Table 1*), which is used to quantify the level of consciousness of trauma patients. This is done by assessing (a) active opening of the eyes (E score), (b) best motor response (M score) and (c) best verbal response (V score). Summation of the scores on these aspects results in the EMV score, ranging from 3 (minimum / worst score) to 15 (maximum / best score).

The catchment area of the azM includes about 231,000 people. Patients were first seen by an emergency room physician, after which a neurologist was consulted in the case of head injuries with clinical signs of brain injury.

Patients with a minor brain injury were usually discharged with a printed waking advice after having been examined at the azM Emergency Room. For the purpose of the present study, we assumed that patients with minor injuries would have returned if they had suffered any complications. Admittance of patients with minor brain injury was indicated when risk factors like skull fracture, persistent amnesia or problems implementing the waking advice (for example single-person household) were present. Patients with moderate and severe brain injuries were as a rule admitted for observation.

To find out how many patients with a THBI were seen in the emergency room, a survey was made by means of a purpose-designed registration form, which was filled out for every patient seen in the department, combined with a chart review. Because visits to the emergency room are not registered as admittance or

Table 1. Definitions of severity of traumatic head and brain injury.

Severity	Criteria
Trauma Capitis without brain injury	GCS score 15, no PTA, no LOC
Mild traumatic brain injury	GCS score 13-15 (if 15: at least PTA or LOC)
Moderate traumatic brain injury	GCS score 9-12
Severe traumatic brain injury	GCS score 3-8

GCS= Glasgow Coma Scale.
PTA= Post Traumatic Amnesia.
LOC= Loss of Consciousness.

discharge, these patients were not coded on the basis of the 'International Classification of Diseases' (ICD), while admitted patients were registered by the Hospital's Registration Office and classified by ICD codes (800, 801, 803, 804, 850-854). Missing data from these patients was added from chart reviews. The data file was further supplemented by comparisons with the requests for radiological evaluation made during the research period, which we received from the Radiology Department. This resulted in the addition of some patients who had been missed. To get an impression of the number of patients belonging to other catchment areas, an a-selective sample of 100 patients was taken to verify their place of residence.

RESULTS

During the period of data collection, 26,464 patients were seen at the emergency room of the azM. Of these, 1933 (7%) had a THBI. The files of the Radiology Department revealed an additional 31 requests for post-traumatic skull X-rays for patients not yet included in the registration (i.e., head injury had not been entered on the original emergency room form). We concluded that these patients had suffered a traumatic head injury without brain injury since no neurologist had been consulted in any of these cases.

The average age of the group as a whole was 30 years (range: 0-97 years); 557 patients (29%) were below the age of 15. The group included 1297 men (67%) and 636 women (33%) *(fig 1)*. The incidence of THBI was 837/100,000 inhabit-

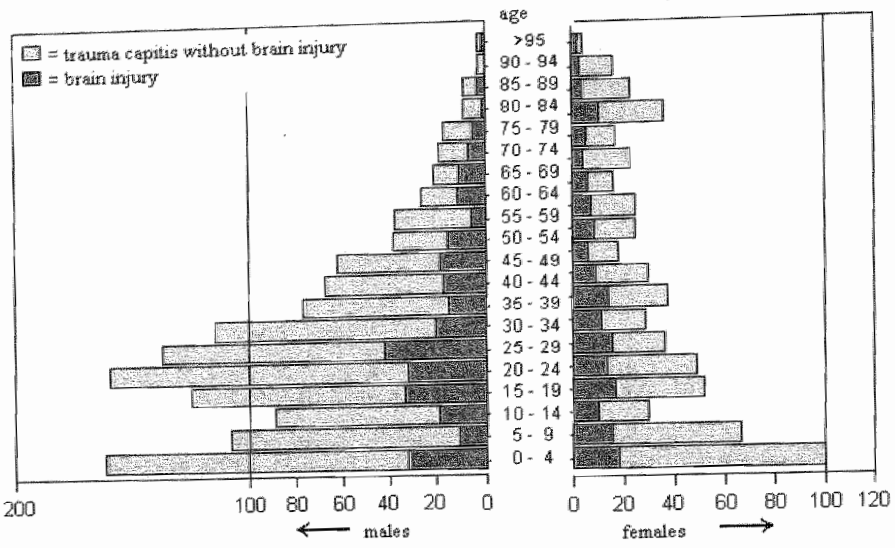

Fig 1. Number of patients with traumatic head and brain injury presenting at the emergency room of the University Hospital Maastricht in 1997.

ants. Of the 1933 patients, 1440 (74%) had no brain injury (trauma capitis), while 493 did have a brain injury. Traumatic brain injury was further subdivided into mild in 467 patients (95%), moderate in 7 (1%) and severe in 19 (4%). An X-ray of the skull was made in 284 cases (15%); fractures (or strongly suspected fractures) were seen in 21 patients (7%).

Causes of the head or brain injury *(Table 2)* included falls (43% of cases), traffic accidents (22%), assaults (15%), sports (7%) and accidents at work (4%). The remainder of the patients (9%) had other causes (for example collapse) or the cause could not be retrieved.

Of the total of 1933 patients, 204 (11%) were admitted to the hospital (*table 2*). The incidence of admittance was thus 88/100,000 inhabitants. Seven patients with a severe traumatic head or brain injury died in the hospital (of whom one in the emergency room): two of these patients had a subdural haematoma, one an epidural haematoma, one elevated intracranial pressure and one diffuse brain injury; two had been shot through the skull. Two patients with a subdural

Table 2. Causes and admission rate of traumatic head and brain injury.

Severity		n	Cause						Admission
			Fall	Traffic	Work	Sports	Assault	Other / ?	
	TC	1440 (75%)	690 (47%)	209 (16%)	64 (4%)	102 (7%)	230 (16%)	145 (10%)	23 (2%)
Mild	TB	467 (24%)	142 (30%)	203 (43%)	15 (3%)	26 (6%)	49 (11%)	32 (7%)	157 (34%)
Moderate	TB	7	3 (43%)	3 (43%)	-	-	1 (14%)	-	6 (86%)
Severe	TB	19	3 (16%)	10 (52%)	-	-	2 (11%)	4 (21%)	18 (95%)
Total		1933 (100%)	838 (43%)	425 (22%)	79 (4%)	128 (7%)	282 (15%)	181 (9%)	204 (11%)

TC = trauma capitis (head injury without brain injury).
TB = traumatic brain injury.

Table 3. Incidence of traumatic head and brain injury in different countries.

Country	Year	Incidence /100,000	Admission rate / 100,000
England [9]	1972	-	270
Scotland [3]	1974-6	-	313
Scotland [10]	1985	1967	-
France [11]	1986	-	281
Spain [12]	1988	-	91
Sweden [13]	1984	-	249
Italy [14]	1984-5	849	372
Norway [15]	1993	229	169
Denmark [16]	1997	-	235
US [17]	1985-7	793	132
US [6]	1991	618	158
Netherlands	1997	836	88

haematoma did not die. All other patients did not have intracranial changes that needed neurosurgical intervention. Of an a-selective sample of 100 patients for whom we checked general patient information, 21 were found to be resident outside the azM catchment area.

DISCUSSION

The interpretation of data from the literature about the incidence and prevalence of minor traumatic head or brain injury is complicated by differences in definitions, criteria for admittance and the structure of the health care system in different countries. Frequencies of admittance mostly reflect hospital policies, while death rates concern only small proportions of the total group of patients. The number of patients seen in the emergency room can be regarded as the most reliable source for estimating the incidence of traumatic head and brain injury. Earlier publications show that approximately 75% of patients with brain injury seek medical attention (15% from the general practitioner, 35% at the emergency room, 25% admitted to hospital). (6) Of the total population visiting the azM emergency room in 1997, 7% had a traumatic head or brain injury. Of these injuries, 99% were classified as minor (the sum of trauma capitis and minor brain injury cases). Of the total group with traumatic head or brain injury, 26% suffered from brain injury.

Table 3 shows the incidence of traumatic head or brain injury in our study compared with the numbers from other studies.(3,6,9-17) The highest incidence in Europe was found in Scotland (1967/100,000).(10) Sosin et al reported an incidence of 618 minor head or brain injuries per 100,000 inhabitants per year in the United States.(6) The total incidence of traumatic head or brain injury in the United States was estimated in the 'National Health Interview Survey 1985/87' as 793 per 100,000 per year.(17)

The incidence of admittance in our study was low compared to that reported in other studies (88/100,000). The reason is probably that the patients seen at the AZM with minor injury are often discharged home with a printed waking advice. The fact that none of the patients sent home returned with complications leads to the conclusion that this admission policy is adequate.

The most common causes of traumatic head injury reported in the literature are falls, traffic accidents and violence,(1,17) which is in agreement with our results (43%, 22% and 15%, respectively). It is striking that 50% of the moderate and severe brain injuries in our study were caused by traffic accidents; this percentage was substantially lower for the group as a whole.

The a-selective sample of 100 patients showed that 21% of the patients were resident outside the catchment area; this group consisted largely of tourists and

university students. This has probably led to an (age-specific) overrating of our calculated incidence. Conversely, this percentage is probably partly compensated by patients from the adherent population who visit hospitals in other catchment areas with a traumatic head or brain injury. The magnitude of this group, however, is unknown. Because the data from the present study was corrected for several other sources of error, our data may be assumed to be reasonably reliable.

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CHAPTER 3

MANAGEMENT OF MILD TRAUMATIC BRAIN INJURY

Lack of Consensus in Europe

Presented at the III meeting of the European Federation of Neurological Societies; September 19-25, 1998; Seville

Adapted from:
J. de Kruijk, P. Leffers, S. Meerhoff and A. Twijnstra.
Management of mild traumatic brain injury: lack of consensus in Europe. *Brain Inj 2001*;15(2):117-124.

ABSTRACT

Mild traumatic brain injury (MTBI) accounts for most of traumatic brain injuries and is an important cause of morbidity. Recent studies in various European countries have shown that no consensus exists about management of patients with MTBI. This study describes the management of MTBI patients in various European hospitals. A short questionnaire covering the areas of interest was sent to several EFNS members in European countries. The results of the inquiry show that there is at present no consensus about criteria for, or management of MTBI in European hospitals.

INTRODUCTION

Over the past 25 years, interest in the management of severe brain injury has increased. In contrast, mild traumatic brain injury (MTBI) is attracting much less attention, despite the fact that MTBI accounts for 80-90% of cases of traumatic brain injury.(1, 2) MTBI is an important cause of morbidity, especially in young people. Recent studies in the Netherlands, Germany and Norway have shown that no consensus exists about indications for the use of radiodiagnostics or about the management of patients with MTBI.(3-5) The present study describes the management of MTBI patients in various European hospitals. The results may be useful as background information for the development of guidelines for the management of MTBI in Europe. Development of such guidelines was proposed at a special workshop during the third meeting of the European Federation of Neurological Societies (EFNS) in Seville, October 1998.

METHODS

A short questionnaire was designed to cover the areas of interest for our study *(table 1)*. There were 5 main topics: 1. diagnosis and criteria for MTBI, 2. guidelines for management of MTBI, 3. diagnostics in MTBI , 4. hospital admission following MTBI and 5. advice to patients with MTBI. We defined MTBI as: 'closed head injury followed by a Post-Traumatic Amnesia (PTA) lasting less than 1 hour and/or loss of consciousness (LOC) lasting less than15 minutes'. Although more than one international definition for MTBI is accepted, this definition seems to represent really mild injury as is explained in the discussion. In 1997, the secretary of the 'scientist panel on Neuro-traumatology' of the EFNS sent the questionnaire to at least one member in each European country. A reminder was sent two months later. The EFNS members were also encouraged to send the questionnaire to colleagues in their own country.

Table 1. Inquiry 'Management of patients with mild head injury' sent to EFNS members in different European countries.

① Which diagnosis do you use in patients with closed head injury followed by short PTA (< 1 hour) and/ or short loss of consciousness (<15 min) ?

❑ Brain concussion **❑ Commotio cerebri** **❑ Mild brain injury**

❑ Mild contusio cerebri **❑ Other .....**

② Do you use the following in classification of mild head injury:

Glascow Coma Score	**❑ No**	**❑ Yes ☞ EMV .....**
Post-Traumatic Amnesia	**❑ No**	**❑ Yes ☞ ..... min.**
Retrograde Amnesia	**❑ No**	**❑ Yes ☞ ..... min.**
Loss of consciousness	**❑ No**	**❑ Yes ☞ ..... min.**

③ Are there guidelines concerning management of mild brain injury

• In your hospital	**❑ No**	**❑ Yes**
• In your country	**❑ No**	**❑ Yes**

④ Which investigations do you perform as a rule?

• X-skull	**❑ No**	**❑ Yes**
• X-cervical spine	**❑ No**	**❑ Yes**
• CT-brain	**❑ No**	**❑ Yes**
• MRI-brain	**❑ No**	**❑ Yes**
• EEG	**❑ No**	**❑ Yes**

⑤ Do you admit these patients to the hospital ? **❑ No** **❑ Yes**

⑥ If the patient is not admitted, which advice(s) do you give these patients ?

• home observation program (waking up the patient every hour)	**❑ No**	**❑ Yes**
• to take fully bedrest	**❑ No**	**❑ Yes .. days**
• to take sick leave	**❑ No**	**❑ Yes .. days**
• pain medication	**❑ No**	**❑ Yes .. days**

⑦ Do you control these patients at least once ? **❑ No** **❑ Yes**

⑧ Do you use separate guidelines for children **❑ Yes** **❑ No** **age < .....**

RESULTS

We received 67 questionnaires from 20 European countries *(fig1)*. As a result of the method used to distribute the questionnaires, we could not calculate response rates. Among the questionnaires returned, the various European countries were not equally represented. Some countries were represented by several responders, while other countries were not represented at all. Sixty percent of all responses came from Eastern European countries. Among the Western European countries, we did not receive any responses from Spain or Ireland. The diagnostic terminology used for MTBI varied. 'Commotio cerebri ' was widely used (54%), followed by 'Mild brain injury', 'brain concussion' and 'mild contusio cerebri' (fig 2). GCS, with cut-off levels between 10 and 15, was used as a clinical criterion for defining MTBI by 64% of responders. Length of LOC, with a range of 2 to 60 minutes, was used as a criterion by 60% of the responders. Duration of PTA

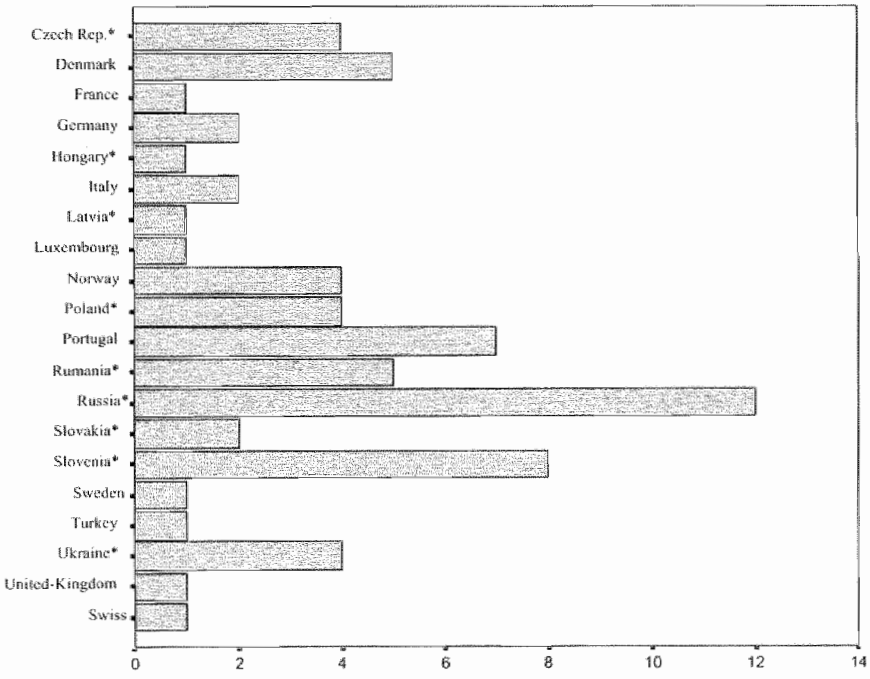

Fig 1. Origin of responders; * = Eastern European country.

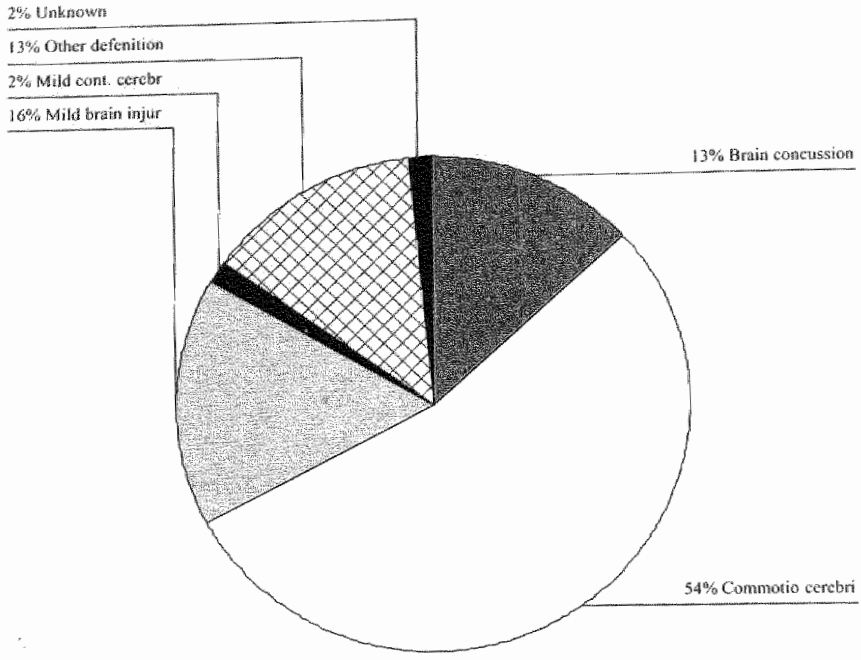

Fig 2. Diagnosis used for closed head injury followed by post-traumatic amnesia lasting less than 1 hour and/or loss of consciousness lasting less than15 minutes.

was used as a criterion by 60% *(table 2)*, with duration varying between 10 and 60 minutes. Diagnostics used *(table 3)*, included radiographs of the skull and cervical spine, performed by respectively 87% and 66% of the responders and CT scan and MR of the brain, performed by respectively 66% and 9 % of all responders. An EEG was ordered by 46% of the responders as part of the diagnostic work-up. Almost all responders (94%) reported admitting patients with MTBI to the hospital for observation. Forty-one percent of responders advised patients to take bed rest for 1 to 14 days *(table 4)*. Sick leave from work was prescribed by 64%, ranging from 1 to 30 days. At least one follow-up visit was considered necessary by 70% of responders. Local in-hospital guidelines for management of brain injury were used by 81% of responders; special guidelines for children were available in 49% of the hospitals. National guidelines were mentioned by 43% of responders.

Table 2. Clinical criteria for mild traumatic brain injury used by responders to the inquiry.

	Yes	No	Unknown	Cut-off values
Glasgow Coma Scale	64%	30%	6%	EMV 10-15
Loss of consciousness	60%	22%	18%	5-60 minutes
Post –traumatic amnesia	60%	19%	21%	10-60 minutes

Table 3. Diagnostics used by responders to the inquiry following mild traumatic brain injury.

	Yes (E/W*)	No (E/W*)	Unknown (E/W*)
Skull x-rays	87% (98% / 69%)	10% (2% / 23%)	3% (0% / 8%)
CT-brain	66% (63% / 69%)	22% (22% / 23%)	12% (15% / 8%)
MRI-brain	9% (12% / 3%)	54% (54% / 54%)	37% (34% / 43%)
EEG	46% (66% / 15%)	31% (22% / 46%)	23% (12% / 39%)
X-rays Cerv. Spine	66% (83% / 39%)	21% (7% / 42%)	13% (10% / 19%)

*E/W = Eastern / Western Europe.

Table 4. Advice, given by responders to the inquiry, to patients with mild traumatic brain injury.

	Yes	No	Unknown	Variation in length
Home observation	60%	16%	24%	
Bedrest	41%	25%	34%	1-14 days
Sick leave	64%	6%	30%	1-30 days
Follow-up examination	70%	30%		

DISCUSSION

1. Diagnosis and criteria for MTBI. Our study shows that there is quite a variety of diagnostic nomenclature for MTBI. Several diagnoses are currently used for the same clinical entity in Europe. Notwithstanding the improvement in the accuracy of MTBI classification on the basis of GCS, PTA and duration of LOC at presentation, our questionnaire showed that a considerable number of responders failed to use these diagnostic criteria. In the medical literature, MTBI is defined by a GCS of 13-15 and a PTA shorter than 24 hours.(6-8) More

recently, the range of GCS was limited to 15, based on the absence of abnormalities in brain-CT of patients with GCS 15.(1, 9) Because, by definition, a GCS of 15 means no ongoing PTA, a short PTA (< 1 hour) is suggested for real mild brain injury.(8) The term minor brain injury has also been suggested for this.(10) As long as no consensus exists about the criteria to be used for MTBI, comparing results of various studies concerning the incidence and management of MTBI remains impossible

2. Guidelines for management of MTBI. Although most responders use in-hospital guidelines for the management of adult patients with MTBI, half of them did not have special guidelines for children. National guidelines were reported to exist in 12 of 20 countries; but in only 6 countries did all responders report the existence of guidelines. A future European consensus would hopefully lead to uniform guidelines in all European countries.

3. Diagnostics in MTBI. Diagnostics used following MTBI aim to discover possible traumatic intracranial complications, especially epidural haematomas. The large number of MTBI patients and the low prevalence of epidural haematomas, has led to much debate about indications for skull radiography. Over the last decade, several authors have suggested various guidelines for performing plain skull radiographs or CT-scans of the brain following MTBI.(2, 9-11) An early CT scan, if available, seems preferable to skull radiography.(11) The results of the present study show that many colleagues still use plain skull radiographs in the management of patients with MTBI. This method was used more frequently in Eastern European countries than in Western European countries (97% and 69% respectively). More than half of all responders (66%) used CT of the brain, while some performed both. A few responders (all from Denmark) perform neither plain skull radiographs nor CT of the brain. The preference of Eastern European responders for plain skull radiography cannot be explained from a lack of availability of CT-scan equipment, because this diagnostic method was used by almost the same numbers of responders in Western and Eastern European countries (63% and 69%). It has been proposed that performing radiographs of the cervical spine in head-trauma patients is only useful in the case of neck pain and/or neurological abnormalities.(12) Nevertheless, 83% of Eastern European responders, and 39% of Western European responders performed cervical spine radiographs. Although according to current views, there is no indication for performing EEG in MTBI patients,(13) almost half of the responders

performed an EEG (66% of Eastern European responders and 15% of Western European responders).

4. Admission following MTBI. Although the incidence of patients admitted to hospitals with MTBI in Europe is not known, the present study shows that many patients with MTBI are being admitted. Admission rates of MTBI patients can be reduced by using guidelines for admission.(14, 15) Clinical observation seems useful only in patients with depressed level of consciousness, evidence of skull fracture, difficulty in clinical assessment because of alcohol, drugs or age and lack of a responsible carer.

5. Advice to the patient. Almost two-thirds of the responders gave 'home observation instructions' to patients with MTBI. These instructions were given to detect intracranial haematomas during the first 24 hours following brain injury and should be given in writing and/or verbally to a responsible person accompanying the patient.(16) Compliance with the advice is probably low.(17) Patients with MTBI who are discharged from the emergency department should also receive advice regarding activities in the immediate future. As our results show, sick leave is prescribed more frequently than bed rest. The majority of responders performed at least one follow-up examination for patients with MTBI. Guidelines concerning mobilisation following MTBI are meant to prevent the development of post-traumatic complaints. Scientific proof of the efficacy of bed rest and sick leave on the development of post-traumatic complaints is insufficient. If there is any effect of bed rest and sick leave, there is some evidence that the effect is better when it is limited to a few days instead of a few weeks.(18) Other studies have indicated that guidelines for treatment and information about the severity of complaints and prognosis can result in the prevention of post-concussional complaints.(19)

CONCLUSION

Notwithstanding the unequal representation of the various European countries in this study, it is clear that there is currently no consensus about management of MTBI in European hospitals. Guidelines for the management of MTBI should be developed by a European group and should be preceded by consensus about criteria for diagnosing MTBI. To create optimal support for the future imple-

mentation of guidelines, it is important that representatives of various professions involved in MTBI management should participate.

ACKNOWLEDGEMENT

The authors thank Professor Franz Gerstenbrand, Chairman of the Scientist Panel on Neurotraumatology of the European Federation of Neurological Societies in 1998, for the distribution of the questionnaires.

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CHAPTER 4

S-100B AND NEURON-SPECIFIC ENOLASE IN SERUM OF MILD TRAUMATIC BRAIN INJURY PATIENTS

A comparison with healthy controls

Presented at the 51st annual meeting of the American Academy of Neurology; 1999; Toronto: Canada

Adapted from:
Kruijk de J, Leffers P, Menheere P, Meerhoff S, Twijnstra A.
S-100B and neuron-specific enolase in serum of mild traumatic brain injury patients; A comparison with healthy controls. *Acta Neur Scand* 2001;103(3):175-179.

ABSTRACT

Objectives: The aim of the study was to determine whether serum concentrations of Neuron-Specific Enolase (NSE) and S100-B in Mild Traumatic Brain Injury (MTBI) patients are higher than in serum of healthy controls.
Material and methods: Blood samples from 104 MTBI patients were taken shortly after the trauma for measurement of S-100B and NSE in serum. In 92 healthy persons these markers were also measured. Marker concentrations in serum of patients and controls were compared. In the patient group the relation between serum-marker concentrations and clinical symptoms and signs, that occurred shortly after the traumatic event, were evaluated.
Results: Median NSE concentration was only slightly higher in patients (9.8 µg/l; 10 to 90 percentile range 6.9 to 14.3µg/l) than in controls (9.4 µg/l; 6.3 to 13.3 µg/l). Median S-100B concentration was significantly higher in patients (0.25 µg/l; 0.00 to 0.68 µg/l) than in controls (0.02 µg/l; 0.00 to 0.13 µg/l). An association was found between S-100B concentrations and vomiting in patients.
Conclusions: S-100B is a useful marker for brain damage in MTBI patients and seems to be associated with the presence of vomiting after the trauma.

INTRODUCTION

Neuron Specific Enolase (NSE) and S-100B in serum and cerebrospinal fluid have been reported to be markers of cell damage of the human central nervous system.(1, 2) NSE is an iso-enzyme of enolase and is localized mainly in neurons but also in smooth muscle fibers and adipose tissue.(3) S-100 is an acidic calcium-binding protein found in the brain as the iso-forms S-100B (95%) and S-100A (5%).(1) S-100B is found in high concentrations in glial cells and Schwann cells and is highly specific for lesions of the central nervous system.
After brain tissue damage, increased concentrations of NSE and S-100B can be measured in peripheral blood serum.(5,6) Serum S-100B and NSE concentration peaks are measured within 6 hours following traumatic brain injury, and these concentrations seem to reflect the severity of the mechanical disruption of the brain tissue.(6-10) Serum S100-B concentrations shortly after severe brain injury do not only correlate with radiological abnormalities and clinical parameters such as the Glasgow Coma Scale score (GCS) and Marshall classification , but also with the Glasgow Outcome Scale. (7, 9) An association between early serum NSE concentrations and survival after severe head injury has been found by Yamazaki.(11) Woertgen found no association between NSE concentrations and the Glasgow Outcome Scale.(7)
The above studies related to severe brain injury, while most brain injury patients are classified as having mild traumatic brain injury (MTBI). In contrast to severe traumatic brain injury, not much is known about the pathophysiology and natural history of MTBI. Traumatically induced axonal damage (TIAD) is hypothised to be the pathophysiological mechanism in MTBI.(12) Biochemical markers confirming TIAD may be helpful in measuring the severity of brain damage. Indeed, elevated S-100B and NSE concentrations have been reported in MTBI(10, 13). However, the patient groups previously studied have been small and no control groups without brain injury were included.
The objectives of the present study were: 1) to measure whether serum concentrations of NSE and S-100B are elevated early after the onset of MTBI and 2) to study the association between serum concentrations and the presence of acute clinical symptoms in MTBI patients.

DESIGN AND METHODS

Patients were eligible for this study if they met the following criteria for MTBI: 1) a blunt blow to the head resulting in post-traumatic amnesia (PTA) of less than 1 hour; 2) initial loss of consciousness (LOC) of less than 15 minutes; 3) GCS must be >13 on presentation at the emergency department and 4) absence of focal neurological signs.

Approval from the ethical committee review board was obtained prior to the study. During 1997 and 1998, all patients presenting with MTBI at the emergency department of the Maastricht University Hospital were examined. Duration of PTA and presence of transient LOC were estimated on information from patient and witnesses. If patients arrived at the emergency department within 6 hours following the trauma and met the criteria for MTBI, informed consent was asked for taking bloodsamples. Patients with alcohol abuse were excluded. Blood samples for NSE and S-100B measurement were taken within 6 hours after the trauma. The cause of the accident, sex, age and the presence of headache, nausea, vomiting and dizziness at first examination were recorded. Presence of traumatic injuries to limbs, trunk or head were also recorded.

A group of 91 blooddonors without a history of traumatic brain injury in the past weeks were used as controls. Serum samples from these volunteers were obtained after informed consent.

All collected samples were sent immediately to the laboratory. The samples were allowed to clot and were centrifuged at 4000 g for 20 minutes at 4°C. The serum was separated from the clot and stored at -20°C until analysis. NSE was measured using a commercially available radioimmunoassay (Pharmacia NSE RIA, Pharmacia & Upjohn, Uppsala, Sweden). This is a double antibody radioimmunoassay in which the NSE from the sample competes with a fixed amount of ^{125}I-labelled NSE for the binding sites on an antibody raised in a rabbit. Separation between the bound and free fractions is obtained by the addition of a decanting suspension composed of Sepharose coated with sheep anti-rabbit antibody followed by centrifugation. The radioactivity of the pellet is inversely proportional to the quantity of NSE in the sample. The assay is calibrated by the manufacturer against purified NSE. The detection limit of the assay is better than 2 µg/l. The total (intra-and inter-assay) coefficient of variation

depends on the concentration, but is typically better than 7.5% at 6 μg/l, 4.7% at 19 μg/l and 8.4% at 90 μg/l.

S-100B was measured using a commercially available immunoluminometric assay (LIA-mat Sangtec 100, Sangtec Medical, Bromma, Sweden). Polystyrene tubes were coated with mouse monoclonal antibody versus S-100B. The S-100B from the samples react with this antibody during the first incubation. Next, all unbound material was removed by a washing step. During the following incubation a second labelled monoclonal antibody, directed against a different epitope reacted with the bound S-100B, forming a sandwich structure. Once again all unbound material was washed away. The label consisted of an isoluminol derivative that is covalently bound to the second antibody. In alkaline solutions containing hydrogen peroxide the label emits a brief flow of photons, which was quantified in a luminometer. The light signal measured in RLUs (relative light units) was directly proportional to the amount of S-100B present in the sample. The detection limit of the assay is better than 0.03 μg/l. The total (intra- and inter-assay) coefficient of variation depends on the concentration, but is typically better than 10% at 0.13 μg/l, and better than 4% from 0.7 up to 20 μg/l.

Statistical analysis was done using SPSS 8.0. Distributions of serum concentrations of S-100B and NSE were visually evaluated in patients and controls. Especially S-100B showed non-Gaussian distributions. Accordingly, Wilcoxon's rank sum test was used for statistical testing of the difference in serummarker concentrations between subgroups. Associations of S-100B and NSE concentrations with age were evaluated using simple linear regression analysis. For the estimation of the serum concentration difference between patients and controls, adjustment for the incomparability in age and sex distributions between these groups was carried out using multiple linear regression analysis. Results are presented as the corrected difference between patients and controls (d) and the associated 95% confidence intervals (CI).

RESULTS

A) Serum markers in controls and patients. Mean age of the 91 recruited controls was 40 years; 14% were female and 86% were male (*table 1*). Median NSE and S-100B serum concentrations in controls were 9.4 μg/l and 0.02 μg/l, respec-

Table 1. Descriptives of MTBI patients and controls.

	Controls	Patients
N	91	104
Gender		
Male	86%	57%
female	14%	43%
Age (in years)		
Mean	40	36
Median	40	36
Range	17– 63	15-76
SD	14	16
S-100B serum conc (in µg/l)		
Mean	0.05	0.31
median	0.02	0.25
10 and 90 percentile	0.00 and 0.13	0.00 and 0.68
SD	0.07	0.24
NSE serum conc (in µg/l)		
Mean	9.6	10.2
Median	9.4	9.8
10 and 90 percentile	6.3 and 13.3	6.9 and 14.3
SD	2.47	3.09

tively. Means and percentiles are shown in *table 1*. No association was found between NSE and S-100B concentrations (r =0.119; p=0.26). A significant association between NSE and age was found (Reg coeff.= 0.07 µg/L.yr; 95% CI: 0.03-0.11). There was no association between S-100B and age. Median S-100B concentration was higher in female than in male controls (0.05 versus 0.00 µg/L; p=0.006). The median NSE concentration in serum of male controls was higher than in serum of female controls (9.7 versus 7.6 µg/L; p=0.037).

104 MTBI patients were included in the study. Causes of trauma included traffic accidents (47%), accidents in and around the house (19%), accidents at work (12%), sports accidents (8%) and battering (8%). In 7%, of cases the cause of trauma was unknown. Mean age was 36 years; 43% were female and 57% male *(table 1)*. Median NSE and S-100B serum concentrations in patients were 9.8

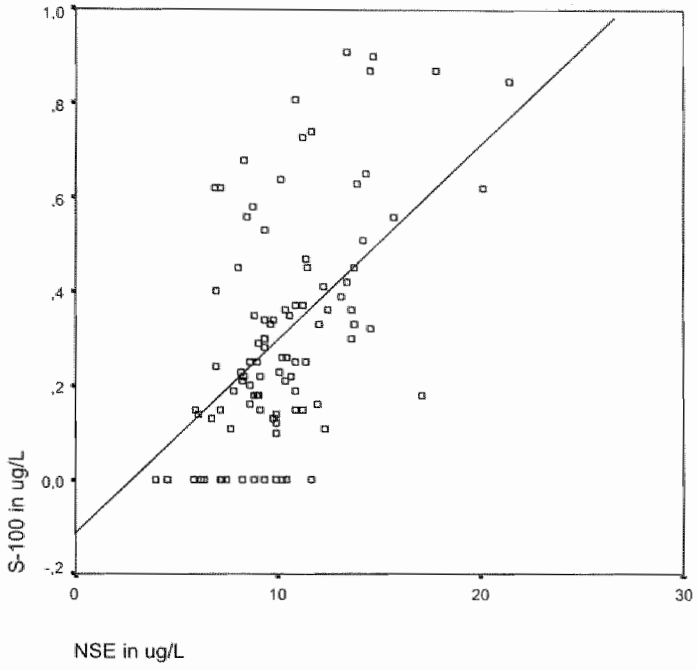

Fig 1. Correlation of serum NSE and S100-B concentrations in patients within six hours after a mild traumatic brain injury.

µg/l and 0.25 µg/l respectively. Means and percentiles are shown in *table 1.* A statistically significant correlation was found between NSE and S100 serum concentrations (r = 0.5; p=0.0001 for Spearmann's rho) in MTBI patients *(fig. 1)* NSE concentrations in patients were significantly higher than in controls after correction for differences in age and sex distributions between the groups (d=0.87 µg/l; 95%CI: 0.01-1.74). S-100B concentrations were also significantly higher in MTBI patients than in controls (d=0.26 µg/l; 95%CI: 0.21-0.31). This difference did not change after correction for age and sex (d=0.23 µg/l; 95% CI: 0.18-0.29).

In order to assess the potential diagnostic relevance of the markers, the distribution of serummarkers concentrations in patients and in controls are given in *fig3.* The distribution of NSE concentrations in patients and controls showed considerable overlap *(fig 2A)*. The overlap for S-100B was much smaller *(fig 2B)*.

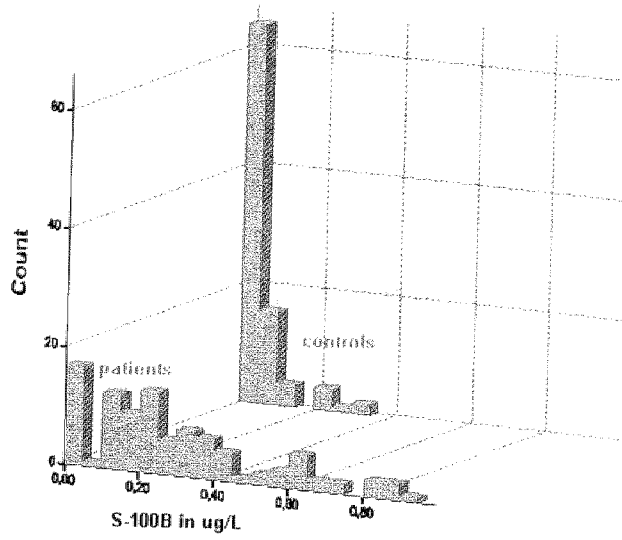

Fig 2A. S-100 B serum concentrations in controls and mild traumatic brain injury patients.

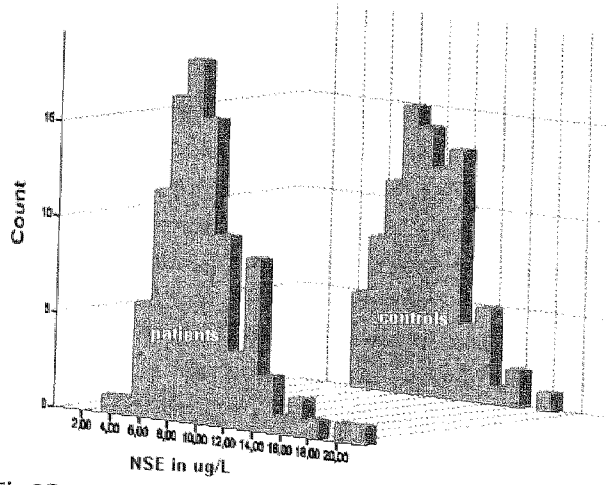

Fig 2B. NSE serum concentrations in controls and mild traumatic brain injury patients.

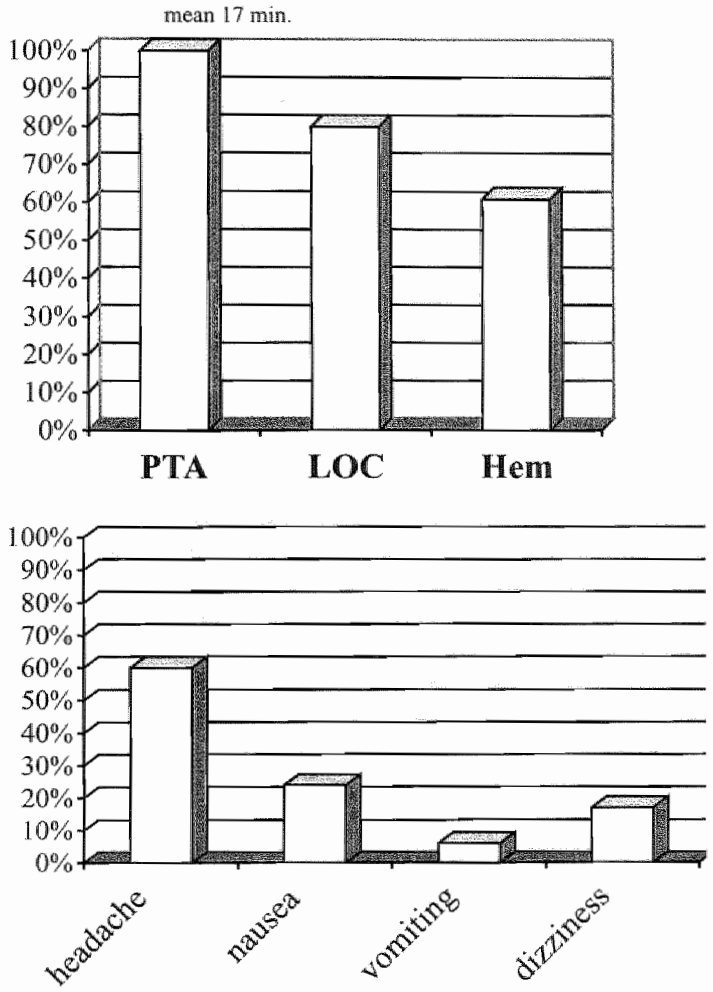

Fig 3. Trauma features (fig 3A) and acute symptoms (fig 3B) in patients with mild traumatic brain injury.
(PTA = post-traumatic amnesia, LOC = loss of consciousness, Hem = hematoma's of limbs, trunk and/or head)

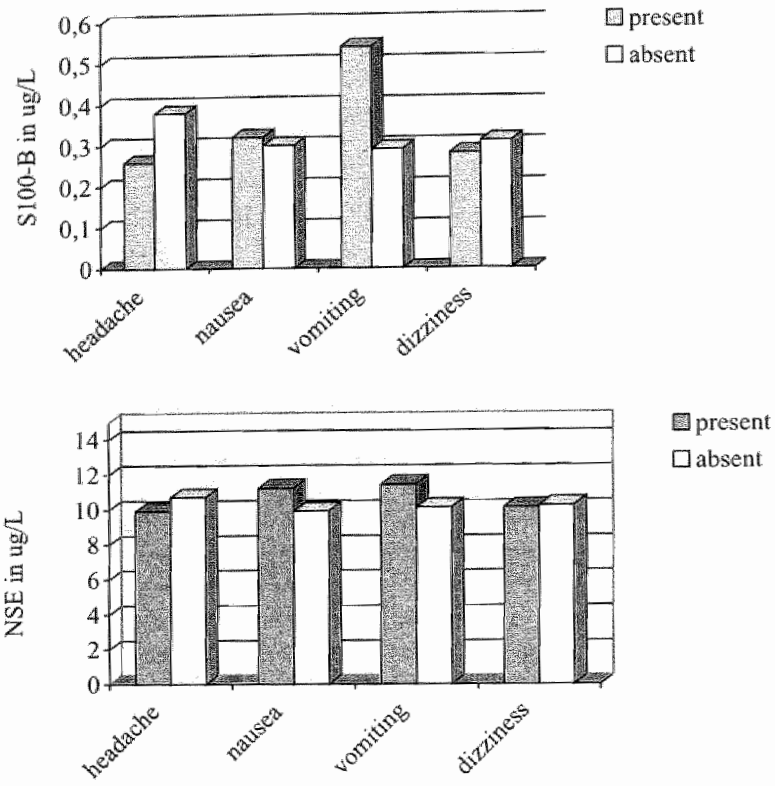

Fig 4. Biochemical marker concentrations and acute symptoms in patients with mild traumatic brain injury.

B) Symptoms and serum markers in patients. Mean PTA was 17 minutes, and transient LOC was reported in 80% of patients. 61% of patients were diagnosed with hematoma's of limbs, trunk and/or head (*fig 3A*). Headache, nausea, vomiting and dizziness at first examination after the trauma was reported in 61%, 24%, 6% and 17% of cases respectively (*fig 3B*).

No association was found between serum marker concentrations and either length of PTA, reported LOC or the appearance of hematoma's to limbs, trunk and/or head. There was no association between the serum-marker concentrations and the symptoms nausea and dizziness (*fig 4*). Patients who vomited

however, had a higher median S100-B concentration than patients who did not (0.5 μg/l vs 0.25 μg/l; p=0.03). Patients with headache however had a lower median S-100B concentration than patients without headache. (0.21 μg/l vs 0.33μg/l; p=0.02).

DISCUSSION

The present study investigated serum NSE and S-100B concentrations in a group of patients with clearly defined MTBI and a group of non-trauma controls. Distribution of age, sex and cause of accident in our patient group were simular to those in other MTBI studies. The mean serum S-100B concentration (0.31 μg/l) in patients in the present study was equal to what was found by Rothoerl in MTBI patients (defined as a GCS >12).(8) Although Ingebrigtsen reported no mean S-100B concentration in his study of 50 patients with MTBI (defined GCS 13-15), he found that concentrations were higher than 0.5 μg/l in 20% of cases(10 of 50). In the present study, 21% (22 of 104) of S-100B values were higher than 0.5 μg/l. The results with regard to serum S-100B correspond with those of earlier MTBI studies, even though the criteria used for MTBI in the present study were stricter. This may be due to the fact that only a small fraction of patients in studies with more liberal criteria did not meet our stricter criteria.
There are no studies available in the medical literature allowing a comparison of NSE serum concentrations in MTBI patients with the mean concentration found in the present study (10.2 μg/l). However, in his study of patients with severe traumatic brain injury (GCS<9), Woertgen found a clearly higher mean serum NSE concentration (30.2 μg/l).(7) Skogseid reported elevated NSE concentrations (>10 μg/l) in 31% (13 of 42) of MTBI patients (GCS 13 -15).(10) In the present study, 44% (47 of 107) of the NSE concentrations measured were higher than 10 μg/l. This difference is hard to explain, given the fact that the criteria for MTBI in the present study were stricter than those in Skogseid's study.
The present study shows that the median serum S-100B concentration in a group of MTBI patients was clearly elevated compared to that in a group of healthy persons. A much less pronounced difference was found between the mean serum NSE concentrations in MTBI patients and controls. No association between serum-marker concentrations and traumatic damage to limbs, trunk and/or head

was found. This finding makes it unlikely that damage to soft tissue or even peripheral nerves are responsible for the elevated serum-marker concentrations. Given the fact that the elevated serum marker concentrations is a consequence of brain injury, we can conclude that damage to brain tissue can be demonstrated even following MTBI, as defined in the present study. The distribution of NSE concentrations in patients and controls showed considerable overlap while the overlap for S-100B was much smaller. As a consequence, determination of S-100B serum levels may prove to be a useful test for the presence of brain damage after MTBI, whereas increased serum NSE levels do not seem to be specific enough for MTBI to be useful for this purpose.

Keeping in mind that S-100B is a marker of damage to glial and/or Schwann cells, while NSE indicates damage to neurons, brain damage after MTBI is more likely to be localized in white matter than in gray matter. Since white matter is covering the axonal structures, this conclusion seems in accordance with the hypothesis that TIAD is an important pathophysiological mechanism in MTBI. The median S-100B concentration of the 6 patients who vomited after the trauma was significantly higher than the median S-100B concentration of those patients who did not. No association was found between clinical parameters nausea, dizziness and serum marker concentrations. In a recent study, Nee concluded that post-traumatic vomiting was associated with a fourfold increase in the risk of a skull fracture.(14) Both, severity of damage to the brain and fracture of the skull, depend on the impact of the trauma. If S-100B is a marker for severity of brain damage, both studies show the relationship between the impact of the trauma and post-traumatic vomiting after MTBI. We have no explanation for the fact that S-100B serum concentration was decreased among patients with headache. In conclusion, S-100B is a potentially useful marker for brain damage in MTBI. A follow-up study to determine the predictive value of serum markers for the occurence of post-concussional complaints is in progress.

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CHAPTER 5

OLFACTORY FUNCTION AFTER MILD TRAUMATIC BRAIN INJURY

Presented at the 53rd annual meeting of the American Academy of Neurology; 2001; Philadelphia, USA

Adapted from:
J.R. de Kruijk, P. Leffers, P.P.C.A. Menheere, S. Meerhoff, J. Rutten and A. Twijnstra.
Olfactory function after Mild Traumatic Brain Injury; *submitted*

ABSTRACT

Olfactory dysfunction after mild traumatic brain injury (MTBI) has not been described before. The present study estimated the prevalence of quantitative olfactory dysfunction after MTBI. Associations of early symptoms and S-100B and NSE serum concentrations with threshold levels of olfactory functions two weeks after MTBI were also examined. The prevalence of olfactory dysfunction two weeks after MTBI was 26%. Mean olfactory threshold level was found to increase with age, at a rate of 0.5 decismel per year. No associations were found between acute parameters of MTBI and olfactory threshold levels.

INTRODUCTION

The occurrence of olfactory dysfunction after traumatic brain injury has been described in particular after skull-base fractures and occipital blows (with frontal impact) to the head.(1-3) It is believed that olfactory information is processed by the olfactory tract via the olfactory bulb to the enthorhinal cortex (primary sensory areas) and the orbitofrontal cortex (secondary sensory areas).(4) Therefore, olfactory dysfunction after traumatic brain injury could not only be a result of shearing of the olfactory nerve filaments,(3) but might also be explained by damage to fronto-temporal cortical structures.

Experimental animal models and post-mortem studies in mild traumatic brain injury (MTBI) patients have shown axonal damage, mainly located in the frontal lobes.(5) These findings were clinically supported by abnormalities on MRI of the brain and elevated serum concentrations of specific markers of brain damage.(6, 7) Confirmation of olfactory dysfunction after MTBI would support the hypothesis that such a relatively mild trauma can nevertheless damage structures of the brain somewhere in, or between, the olfactory nerve filaments and the fronto-temporal cortical structures.

The aim of the present study was to determine the prevalence of olfactory dysfunction 2 weeks after MTBI. Additionally, associations of early symptoms (headache, dizziness, nausea and vomiting) and biochemical serum markers (S-100B and NSE) with olfactory threshold levels were investigated.

METHODS

Participants. The study was conducted at the University Hospital in Maastricht, and the study was approved by the ethics committee of this centre. Each patient provided written informed consent. Patients were eligible for the study if they were at least sixteen years of age and presented at the emergency room within six hours after the trauma. MTBI was defined as a blunt blow to the head resulting in 1) PTA of less than 1 hour; and/or 2) initial LOC of less than 15 minutes; 3) GCS of 14 or 15 on presentation at the emergency department; and 4) absence of focal neurological signs. Patients were excluded if they suffered from multiple trauma

or if there was a need for clinical observation. Patients with a history of traumatic brain injury, alcohol abuse or psychiatric disorder were also excluded.

Quantitative olfactometry. Two weeks after the trauma, olfactory function was quantified using a 'Hyposmia utility kit' (Olfacto-labs®, El Cerrito, US). The test covered nine Phenyl Methyl Ethyl Carbinol (PM-Carbinol) concentrations with ranges of 10 decismels (dS) between –25 and 55 dS. The PM-Carbinol was presented to the patient (with both nostrils open) in a blank sniff bottle together with a blank odourless bottle. The patient had to select the bottle having the stronger odour. The threshold was the lowest concentration for which the patients correctly selected the PM-Carbinol bottle three consecutive times. According to the manufacturers, the normal range of olfactory thresholds (95% of subjects aged 20-70 years) is from –25 to +25 dS. Between the ages of 10 and 70 years, the threshold is said to increase by 0.3 dS per year. Differences between genders and between moderate smokers and non-smokers are negligible. Thresholds in the range of 30-55 dS represent hyposmia for the tested odour and any subject who cannot detect 55 dS is considered to have no olfactory function for this odour.(8)

Study design. If patients fulfilled all admissibility criteria, printed and oral explanations about the study were given by the physician in attendance (neurology resident) and consent was asked for participation in the study. Symptoms at the ER were noted and blood samples for NSE and S-100B measurement were taken within 6 hours after the trauma. NSE and S-100B concentrations were measured using commercially available radioimmuno-assays for NSE (Pharmacia & Upjohn, Uppsala, Sweden) and a immunoluminescenmetric-assay for S100B (Sangtec Medical, Bromma, Sweden). Two weeks after the trauma, patients were seen at the outpatient clinic for quantitative olfactometry.

Analysis. Baseline data, including demographics, symptoms and serum marker concentrations at the ER, were described. Olfactory threshold values at two weeks after the trauma were compared with normal values as provided by Olfacto-labs®. The increase in the olfactory treshold values with age was analysed with linear regression analysis. Finally, the associations between olfactory threshold values at two weeks and individual symptoms and serum marker concentrations at the ER were examined, using multiple linear regression analysis with adjustment for the influence of age.

RESULTS

Between October 1996 and December 1998, we examined 61 males and 50 females with MTBI and no other neurological disorders. Median age was 34 years *(table 1)*. The olfactory threshold values measured two weeks after the trauma *(fig 1)* ranged from –15 to > 55 dS. The normal range of olfactory thresholds (95% of subjects aged 20-70 years) is –25 to +25 dS. Twenty-four of our patients (22%) had threshold values between 30 and 55 dS, defined as hyposmia. Five patients (4%) were even unable to detect 55 dS (anosmia).

Seventy-four patients (66%) gave consent for blood samples to be taken at the ER, and NSE and S-100B concentrations were each found to be elevated in 41% of patients. There was a positive association between age and olfactory thresholds (b=0.48 dS/year; 95% CI: 0.33 - 0.64) *(fig 2)*. After adjustment for age, linear regression analysis of olfactory thresholds at two weeks showed no significant associations with the presence of symptoms at the ER *(table 2)*, nor with early concentrations of S-100B (b= -11 dS per µg/l; 95% CI: -28 – 5dS) or NSE (b= 1 dS per µg/l; 95% CI: -2 – 1dS) in the serum.

Table 1. Patient characteristics assessed at the emergency room.

Demographic characteristics (111 patients)	
Gender	
Female	45%
Age in years	
(median 34; 5-95 percentiles 17-72)	
15-25	31%
26-35	21%
36-45	21%
46-55	12%
56-65	8%
> 65	7%
Presence of symptoms	
Headache	62%
Nausea	29%
Dizziness	18%
Vomiting	6%
Serum markers (74 patients)	
NSE (mean 9.77; SD 2.92)	
≥ *10 µg/l*	41%
S-100B (mean 0.28; SD 0.22)	
≥ 0.3 *µg/l*	41%

Table 2. Difference in olfactory threshold between patients with and without symptoms at the ER.

Symptoms presented at ER	B* (95% CI) §
Headache	1 dS (-5 to 6)
Dizziness	-1 dS (-9 to 6)
Nausea	-2 dS (-8 to 4)
Vomiting	-2 dS (-12 to 9)

* B = difference in olfactory threshold between patients with and without symptoms at the ER: linear regression analysis of outcome variable (Olfactory threshold at two weeks) on acute symptoms after adjustment for age.
§ 95% Confidence interval for B.
dS = decismel.

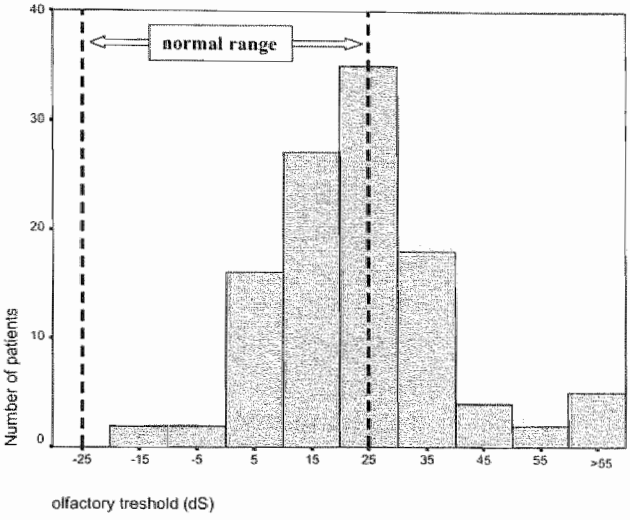

Fig 1. Quantitative olfactory function two weeks after mild traumatic brain injury in 111 patients.

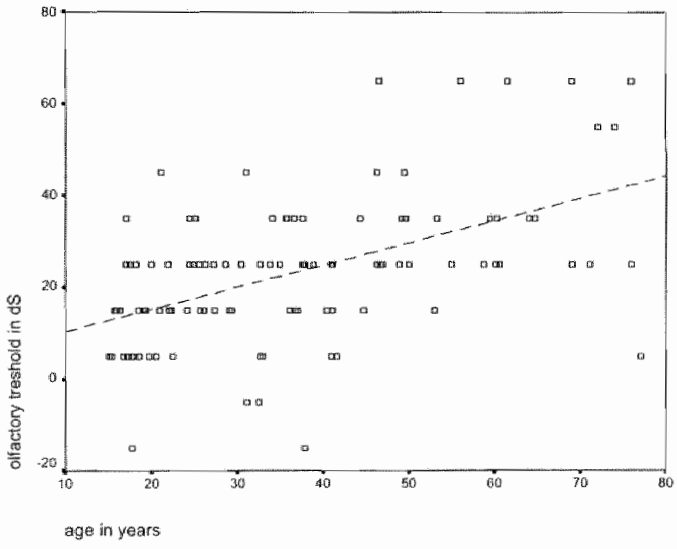

Fig 2. Association between age and olfactory threshold in mild traumatic brain injury patients.

DISCUSSION

We found that a quarter of MTBI patients showed quantitative olfactory dysfunction after two weeks, while 22% showing hyposmia and 4% anosmia. As far as we know, no other prospective studies after MTBI are available to compare these findings with. In a normal population with similar age range, hyposmia has been found in 2% and anosmia has been observed in about 0.2% (data from Olfacto-labs®). With regard to age, we found that the threshold increased by almost 0.5 dS per year, whereas according to the manufacturer of the test, the threshold should increase by 0.3 dS per year in healthy controls. The fact that we found an association with age shows that we did indeed measure olfactory function. These findings support the idea that MTBI causes damage to the brain (olfactory nerve and/or frontal cortical structures). However, even though we found a high prevalence of olfactory dysfunction, we could not detect any correlation between olfactory dysfunction and acute parameters of MTBI. A retrospective study of 29 head injury patients with olfactory dysfunction by Schechter found no association between severity of injury and extent of olfactory dysfunction either.(2) This is surprising since acute MTBI parameters are associated with the severity of other outcome variables such as post-traumatic complaints. (Chapter 6)

One explanation for the unexpected combination of findings could be that olfactory dysfunction is associated with an aspect of the trauma that is unrelated to its acute parameters. Another possibility is that the reference values provided by the manufacturer of the smell test we used are not valid for our population or for the environment in which the test was applied. The test kit had not exceeded its expiration date, nor did we detect any rise in measured thresholds over time. In future research, it is important to check the validity of the reference values by including a healthy local control group.

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CHAPTER 6

PREDICTION OF POST-TRAUMATIC COMPLAINTS AFTER MILD TRAUMATIC BRAIN INJURY

Early symptoms and biochemical markers

Adapted from:
J.R. de Kruijk, P. Leffers, P.P.C.A. Menheere, S. Meerhoff, J. Rutten, A. Twijnstra; Prediction of post-traumatic complaints after mild traumatic brain injury, early symptoms and biochemical markers. *submitted*

ABSTRACT

Aim of the study: Early recognition of mild traumatic brain injury (MTBI) patients who are at risk of developing post-traumatic complaints (PTC) would be useful because early follow-up at the outpatient clinic might help to reduce the severity of these complaints in the long run. The aim of the present study was to identify clinical parameters at first presentation after MTBI that are predictive of the severity of post-traumatic complaints after six months.

Findings: After six months, severity of most complaints had declined to pre-trauma levels but medians for headache, dizziness and drowsiness were still elevated. In a series of 79 patients, 22 (28%) reported one or more PTC after six months. After adjustment for baseline variables, an at least twofold increased severity of all PTC subgroups was reported by those patients reporting headache, dizziness and/or nausea at the emergency room (ER). A twofold increased severity of 'cognitive' and 'vegetative' PTC was also found in those with elevated concentrations of biochemical serum markers (S-100B and NSE) at first presentation. The prevalence of full recovery after six months increased from 50% in patients with three symptoms to 78% in those with no symptoms at the ER. Inclusion of biochemical markers showed that all ten patients with no symptoms at the ER and normal markers recovered fully.

Conclusions: The presence of headache, dizziness and/or nausea at the ER after MTBI is strongly associated with the severity of most PTC after six months. Identifying MTBI patients at the ER without headache, dizziness, nausea or elevated serum marker concentrations may be a promising strategy for predicting good outcome.

INTRODUCTION

Mild Traumatic Brain Injury (MTBI) accounts for about 90% of traumatic brain injuries (1-3). Although the mortality rate is negligible, the frequency of post-traumatic complaints (PTC) is appreciable. The severity of most PTC declines during the first three months, but the prevalence of having any complaints six months after the trauma is still estimated to be 20 to 80% (4-7). These PTC comprise a large number of symptoms, including headache, dizziness, drowsiness, loss of memory and concentration problems. It is believed that these complaints are caused by a combination of brain injury, psychological, emotional and motivational factors.

Educating patients shortly after MTBI at the outpatient clinic about the expected prognosis of possible complications might help to reduce the severity of PTC in the long run (8-10). Since many MTBI patients do not experience persistent PTC at all, reducing needless follow-up will save money and prevent medicalization of these mainly young and healthy people. Against this background, early recognition of patients who are not at risk of persistent PTC would be useful.

MTBI patients have been studied in order to find prognostic indicators of PTC (2, 7, 11). It was found that female sex, more advanced age and prior MTBI are associated with poor outcome. Apart from headache within 24 hours after MTBI, which is also associated with poorer outcome (2, 7), no associations between presenting MTBI symptoms and outcome have been reported.

The predictive value of specific serum markers S-100B and NSE serum concentrations for the Glasgow Outcome Score after severe head injury has been established earlier (12, 13) and elevated NSE and S-100B serum concentrations were also found recently in MTBI patients within six hours after the trauma (14, 15). Although early elevated S-100B and NSE concentrations in serum seem to predict neuropsychological dysfunction (16, 17), the relationship between elevated biochemical marker concentrations and PTC after MTBI has not been studied so far.

The aim of the present study was to identify symptoms and biochemical markers at first presentation after MTBI that are predictive of the severity of post-traumatic complaints six months later. In order to develop a clinically useful test to determine which MTBI patients do not require follow-up at the outpatient clinic, we also tried to find a combination of variables that could predict favorable outcome after six months.

METHODS

Participants. The study was conducted at the University Hospital of Maastricht, the Netherlands, as part of an intervention study on the efficacy of bed rest after MTBI. The study was approved by the hospital's ethics committee and each patient provided written informed consent. Patients were eligible for this study if they were older than fifteen years and presented at the ER within six hours after the trauma. MTBI was defined as a blunt blow to the head resulting in 1) post-traumatic amnesia of less than one hour and/or; 2) initial LOC of less than 15 minutes; 3) GCS of 14 or 15 on presentation at the emergency department; 4) absence of focal neurological signs. Patients were excluded if they suffered from multi-trauma or if there was a necessity for clinical observation. Patients with a history of traumatic brain injury, alcohol abuse or a psychiatric disorder were also excluded.

Predictive variables. The present study assessed the presence of symptoms at the ER (headache, dizziness, nausea, vomiting and neck pain) and biochemical markers (Neuron Specific Enolase and S-100B) in serum taken within six hours after the trauma as possible predictive variables for the severity of PTC. Age, sex and intervention (bed rest within ten days after the trauma) were considered as possible confounders.

Outcome variables. Outcome variables were the severity of 16 PTC six months after the trauma. Selection of these PTC was based on an earlier study which showed that these complaints differed in intensity from those in control subjects (18). The PTC were measured on visual analogue scales (VAS) and divided into four subgroups (cognitive, dysthymic, vegetative, and physical). Complaints assessed in the present study were very similar to the symptoms used in the

Rivermaid Post Concussion Symptoms Questionnaire, which was developed and standardized by the Oxford Head Injury Service (5, 19).

Study design. If patients fulfilled all admissibility criteria, a written and oral explanation about the study was given by the physician in attendance (neurology resident) and consent was asked for participation in the study. The presence of headache, neck pain, nausea, vomiting and dizziness was recorded at first examination. Blood samples for NSE and S-100B measurements were taken within six hours after the trauma. NSE and S-100B concentrations were measured using commercially available immunoluminometric assays (Pharmacia NSE RIA, Pharmacia & Upjohn, Uppsala, Sweden and LIA-mat Sangtec 100, Sangtec Medical, Bromma, Sweden). NSE and S-100B serum concentrations were defined as elevated if they were higher than, respectively, 10 μg/l and 0.3 μg/l. At the follow-up moments (two weeks and six months), all patients were questioned at the outpatient clinic about the severity of PTC. At first follow-up, patients were not only questioned about the severity of PTC at that moment, but also about the severity of these complaints before the trauma.

Statistical analysis. Baseline data including demographics, acute clinical symptoms and serum marker concentrations were summarized. Medians and 5 and 95 percentiles of VAS scores for all PTC were recorded for each follow-up moment. The sums of the VAS scores for the four subgroups of PTC after six months were also calculated and the interrelations between the severity levels of these four PTC subgroups were expressed as Spearman's correlation coefficients.

Because of their non-normal distribution, VAS scores were transformed to their natural logarithms (ln). Associations between PTC after six months and possible predictive variables were estimated by multiple linear regression analysis, adjusting for gender, age and type of bed rest advise after trauma. Variables with a statistically significant association with PTC were selected and predictive values for combinations of these symptoms were calculated. For this purpose, patients were divided into groups 'fully recovered' and 'not fully recovered' after six months. Patients were considered to be 'fully recovered' if the VAS scores of all PTC after 6 months were lower than the 95 percentile of the pre-traumatic VAS scores. If one or more VAS scores after six months were higher than the pre-traumatic 95 percentile, outcome was defined as 'not fully recovered'.

RESULTS

Patient characteristics and acute variables. Between October 1996 and June 1999, 107 MTBI patients were enrolled in the study. After two weeks, 103 patients showed up for follow-up examination (96%), versus 79 (74%) after six months. Baseline variables were described for the 103 patients showing up after two weeks *(table 1)*. Slightly more men than women were included (57% versus 43%) in the study. More than half of the patients (61%) reported headache at the ER. Nausea, dizziness, neck pain and vomiting were reported by 27%, 18%, 17% and 6% respectively. Fourteen patients (13%) did not consent to have blood samples taken at the ER. Eventually, serum markers were measured in 89

Table 1. Patients characteristics at the emergency room.

Demographic characteristics (n=103)	
Gender	
Female	43%
Age in years	
(mean 37.2; 15-75)	
15-25	28%
26-35	20%
36-45	20%
46-55	16%
56-65	9%
> 65	7%
Acute symptoms	
Headache	61%
Nausea	27%
Dizziness	18%
Neck pain	17%
Vomiting	6%
Serum markers (n = 89)	
NSE (mean 9.8 µg/l; 3.9 – 21.4 µg/l)	
≥ 10 µg/l	40%
S-100B (mean 0.28 µg/l; SD 0.02 – 0.90 µg/l)	
≥ 0.3 µg/ L	38%

Table 2. Severity of post-traumatic complaints at different follow-up moments.

VAS ‡ score of post-traumatic complaints	Follow-up moment		
	Before trauma* median (5-95 percentile)	Two weeks (n=103) median (5-95 percentile)	Six months (n=79) median (5-95 percentile)
Cognitive PTC			
Trouble concentrating	0 (0-50)	6 (0-92)	1 (0-80)
Easily overwhelmed by problems	0 (0-45)	0 (0-48)	0 (0-66)
Forgetful	1 (0-45)	10 (0-60)	1 (0-70)
Sum cognitive	7 (0-90)	28 (0-147)	13 (0-186)
Vegetative			
Flushing easily	0 (0-53)	0 (0-41)	0 (0-20)
Feeling short of breath	0 (0-55)	0 (0-63)	0 (0-52)
Feeling faint	0 (0-59)	0 (0-59)	0 (0-53)
Sum vegetative	6 (0-98)	11 (0-186)	5 (0-82)
Dystimic			
Depressed	0 (0-48)	0 (0-54)	1 (0-59)
Drowsy	0 (0-43)	13 (0-94)	3 (0-90)
Crying more easily	0 (0-41)	0 (0-51)	0 (0-19)
Confused	0 (0-22)	1 (0-57)	0 (0-49)
Sum dysthymic	7 (0-101)	31 (0-179)	8 (0-190)
Physical			
Headache	1 (0-59)	12 (0-97)	3 (0-75)
Dizziness	0 (0-32)	12 (0-95)	3 (0-60)
Nausea	0 (0-14)	0 (0-58)	0 (0-26)
Light-headed	0 (0-33)	3 (0-60)	1 (0-60)
Paresthesia of arm(s)	0 (0-29)	0 (0-53)	1 (0-62)
Sleeping problems	1 (0-83)	1 (0-83)	0 (0-57)
Sum rest	18 (0-164)	63 (0-314)	28 (0-233)

‡ VAS = visual analogue scale.
* Measured retrospectively at first follow-up.
PTC = post-traumatic complaints.

Table 3. Correlations (Spearmann Rho) for severity of post-traumatic complaints after 6 months in four subgroups.

Sum of VAS-score of:	Cognitive PTC	Vegetative PTC	Dysthymic PTC
Vegetative PTC	R=0.68*		
Dysthymic PTC	R=0.75*	R = 0.75*	
Physical PTC	R=0.67*	R = 0.72*	R = 0.72*

*Correlation is significant at the .01 level (2-tailed).
PTC = post-traumatic complaints.

Table 4A. Associations between post-traumatic complaints (summed in subgroups) after 6 months and predictors at the emergency room.

Acute parameters	Subgroups of post-traumatic complaints# after six months exp B‡ (95%conf.int)			
	Cognitive	Vegetative	Dystim	Physical
Dizziness	3.8 (1.1-12.8)*	2.6 (0.8-8.0)	3.3 (0.9-12.1)	3.2 (0.9-11.5)
Headache	2.1 (0.9-5.2)	2.9 (1.3-6.5)*	3.1 (1.2-7.9)*	3.2 (1.3-16.0)*
Nausea	2.1 (0.8-5.6)	2.0 (0.8-5.0)	3.7 (1.3-10.1)*	3.9 (1.4-10.5)*
Vomiting	0.9 (0.2-5.3)	0.5 (0.1-2.4)	1.7 (0.3-11.4)	4.3 (0.7-26.8)
Neck pain	0.9 (0.3-3.1)	1.5 (0.5-4.8)	1.0 (0.3-3.76)	0.8 (0.2-2.9)
Elevated S-100	2.0 (0.8-5.0)	1.2 (0.5-2.8)	1.4 (0.5-3.7)	1.5 (0.6-4.0)
Elevated NSE	1.6 (0.5-4.9)	2.0 (0.8-5.5)	1.3 (0.4-4.2)	1.4 (0.5-4.5)

sum of VAS scores in different PTC subgroups.
‡B= Coefficients from linear regression analysis of ln outcome variable (severity of post-traumatic complaints after six months) on acute parameters after adjustment for gender, age and advised bed rest after trauma.
*p<0.05 (two-sided test).

patients. NSE concentrations were elevated in 40% of patients, while S-100B concentrations were elevated in 38% of patients.

Outcome variables. *VAS scores of PTC after two weeks and six months are summarized in table 2.* Forgetfulness, drowsiness, headache, dizziness, trouble concentrating and lightheadedness were the severest complaints after two weeks. After six months, the severity of most complaints had declined to pre-trauma levels, though medians for headache, dizziness and drowsiness were still increased.

Table 4B. Associations between five specific post-traumatic complaints after 6 months and predictors at the acute moment.

Acute parameters	Specific post-traumatic complaints after six months exp B‡ (95%conf.int)				
	Trouble concentrating	Forgetful	Dizziness	Headache	Drowsiness
Dizziness	3.5 (1.2-10.3)*	2.6 (0.9 - 7.1)	1.5 (0.5-4.3)	2.4 (0.9-6.4)	3.8 (1.3 -11.3)*
Headache	2.9 (1.3-6.2)*	1.2 (0.6-2.5)	3.7 (1.9-7.6)*	1.9 (0.9-3.9)	2.4 (1.1-5.4)*
Nausea	2.6 (1.1-6.3)*	1.3 (0.6-3.0)	3.1 (1.4-6.8)*	2.8 (1.3-6.1)*	3.7 (1.3-10.1)*
Utovomiting	0.8 (0.2-4.1)	0.8 (0.2-3.5)	6.8 (1.6-29.0)*	1.6 (0.4-6.6)	1.8 (0.4-9.0)
Neck pain	0.8 (0.3-2.6)	1.1 (0.4-3.2)	0.6 (0.2-1.63)	0.8 (0.3-0.9)	1.0 (0.3-3.3)
Elevated S-100	1.2 (0.5-2.8)	2.2 (1.0-4.9)*	1.2 (0.5-2.6)	1.2 (0.6-2.5)	1.0 (0.4-2.5)
Elevated NSE	1.5 (0.6-4.0)	1.3 (0.5-3.2)	2.3 (0.9-5.6)	2.2 (1.0-5.0)*	1.2 (0.4-3.3)

Sum of VAS scores in different PTC subgroups.
‡B= Coefficients from linear regression analysis of ln outcome variable (severity of post-traumatic complaints after six months) on acute parameters after adjustment for gender, age and advised bed rest after trauma.
*p<0.05 (two-sided test).

Table 5. Presence of symptoms at the ER as a diagnostic test for the presence of post-traumatic complaints 6 months after a mild traumatic brain injury.

Number of symptoms‡ at the ER	Presence of PTC (n=22)	Absence of PTC (n=57)	Prevalence of full recovery
3 (n=8)	4	4	50%
2 (n=13)	5	8	62%
1 (n=31)	7	24	77%
0 (n=27)	6	21	78%

‡ Headache, dizziness and nausea.

Strong correlations were found between the sum scores of all PTC subgroups after six months *(table 3)*.

Associations between acute symptoms and outcome variables. After adjustment for gender, age and advised bed rest, linear regression analysis of ln sum VAS scores of the four PTC subgroups after six months showed an at least twofold increased sum VAS score for all PTC subgroups in those patients reporting headache, dizziness and/or nausea at the ER *(table 4A)*. Twofold increased 'cognitive' and 'vege-

tative' sum VAS scores were found in those with, respectively, elevated S-100B and NSE concentrations.
For patients reporting headache, dizziness or nausea at the ER, linear regression analysis of ln VAS scores for five specific PTC (adjusted for gender, age and advised bed rest) showed an at least twofold increased severity of one or more PTC after six months *(table 4B)*. Vomiting was only associated (sevenfold) with 'dizziness'. A twofold increased severity of 'forgetfulness', 'dizziness' or 'headache' after six months was found in those patients with elevated early serum NSE or S-100B concentrations. No correlation was found between neck pain at the ER and outcome after six months.
Clinical tests to predict outcome. Twenty-two of 79 patients (28%) were classified as 'not fully recovered' after six months. We tested the clinical value of headache, dizziness and nausea at the ER in predicting full recovery after six months. Vomiting was not included because only 6% of the patients suffered this symptom. The prevalence of full recovery increased from 50% to 78% as the number of symptoms at the ER decreased from three to zero *(table 5)*. When we included serum markers of 68 patients as additional variables, full recovery was predicted in all 10 patients with no symptoms and normal serum markers.

DISCUSSION

According to the criteria used in the present study, 28% of patients suffered from one or more PTC six months after MTBI. Using the same set of PTC, Bohnen reported that symptoms in 25% of patients persisted for up to six months (18). Other studies found that 20% - 80% of patients with MTBI did not recover completely within the first year after the trauma (2, 4, 7). This huge variation probably reflects the different definitions of MTBI and the use of different outcome variables in these studies. Cut-off points for the Glasgow Coma Score used to define MTBI ranged from 13-15. Outcome variables used included post-traumatic complaints and/or neuro-psychological test results.
In the present study, MTBI was defined on the basis of the most recent literature (6, 20, 21). The outcome variables in the present study were virtually the same as those used by Bohnen and the Oxford Head Injury Service (5, 18, 19).

Even though there was a strong association between the severity of PTC in the different subgroups, physical complaints scored highest. The finding that headache and dizziness are important specific PTC confirms the findings of previous studies (4, 7, 9, 22, 23). Patients in the present study reported only marginally more 'forgetfulness' and 'trouble concentrating' after six months than the reported pre-traumatic levels. These specific variables, however, were included in the analysis because they had been mentioned as important outcome variables in earlier studies (9, 22, 24, 25).

It was shown that the presence of headache, nausea and dizziness in MTBI patients at the ER is associated with the severity of PTC after six months. Though the presence of headache within 24 hours after the trauma has previously been described as a prognostic factor for outcome after MTBI (2, 7), the relation with nausea and dizziness had not been reported before.

Vomiting was only associated with the subgroup of physical PTC. This seems to be mainly due to the strong association with dizziness. In the literature, a twofold increased risk of skull fractures has been reported for post-traumatic vomiting (26). However, no association between vomiting and severity of PTC has been described before. In our study, the relationship between vomiting at the ER and dizziness after six months might be explained by the occurrence of peripheral vestibular injury (labyrinthal contusion).

Elevated biochemical marker concentrations were only associated with some of the PTC after six months. The fact that S-100B was associated with the severity of cognitive PTC seems to support earlier findings that elevated S-100B is predictive of poorer cognitive functioning (16, 17). Elevated NSE concentrations were positively associated with severity of dizziness and headache after six months. Post-traumatic headache is believed to be mainly muscle related (27). Therefore, the elevated NSE concentrations could originate from damaged muscle tissue.

The presence of neck pain at the ER was not at all associated with PTC after six months. This finding is notable, since complaints reported after whiplash injuries without MTBI are generally similar to those found in the present study (28).

Although headache, nausea and dizziness were strongly associated with severity of PTC after six months, half of the patients with a combination of these three symptoms at the ER still had PTC after six months, whereas the other half of the patients had fully recovered. The prevalence of full recovery increased further in

patients reporting two symptoms (62%) or one symptom (77%). Patients reporting no symptoms at the ER had a 78% chance of full recovery. The negative predictive value increased to 100% when elevated S-100B and NSE concentrations were added to the selection variables. All MTBI patients without elevated serum markers or symptoms at the ER were free of PTC after six months. Although biochemical marker data of 11 patients was missing, this seemed not to explain this finding because slightly more patients in the 'markers missing' group than in the 'markers not missing' group recovered fully (81% and 64%, respectively).

CONCLUSION

The presence of headache, dizziness and/or nausea at the ER after MTBI is strongly associated with the severity of most PTC after six months. The absence of these symptoms in combination with normal serum marker concentrations within six hours after the trauma seems highly predictive of full recovery after six months. Identifying MTBI patients at the ER without headache, dizziness, nausea and elevated serum marker concentrations may be a promising strategy to reduce unnecessary follow-up. However, these results should be verified in future studies.

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CHAPTER 7

GENERIC HEALTH STATUS FOLLOWING MILD TRAUMATIC BRAIN INJURY

INTRODUCTION

Most cases of traumatic brain injury belong to the category of mild traumatic brain injury (MTBI). Beside rare acute intracranial complications and early complaints, the health status of MTBI patients is mostly determined by persistent post-traumatic complaints (PTC). Although it is believed that damage to the brain following MTBI can be demonstrated by neuro-imaging and biochemical serum markers,(1, 2) it is not clear to what extent these complaints are directly caused by brain injury or are rather the result of the trauma experience in combination with psychosomatic, emotional or motivational factors.

During the last decade, many disciplines have been involved in the evaluation of outcome after MTBI. Most studies have evaluated PTC (3-8) or neuro-psychological test results.(5, 8-10) MTBI may represent a 'hidden disability', as a person may seem physically normal, yet have considerable PTC. Information about the negative effect on daily life activities may complement reported PTC in assessing the consequences of MTBI.

Few studies have measured generic health status in MTBI patients. The 36-item short form health survey questionnaire (SF-36) is a widely used generic health status measure. Recently, Paniak et al. found that the SF-36 questionnaire is a sensitive measure of MTBI-related general health effects three weeks after the trauma.(11). The long-term consequences for generic health status have not yet been assessed in MTBI patients. The aims of the present study were: 1) to investigate the generic health status of MTBI patients two weeks, three months and six months after the trauma; 2) to describe the association between the presence of post-traumatic complaints and generic health status six months after the event.

METHODS

Participants. The present study was part of an intervention study on the efficacy of bed rest for MTBI patients. The study was approved by the institutional ethics committee of the Maastricht University Hospital. All patients provided written informed consent.

MTBI patients were eligible for the study if they were older than fifteen years and presented at the emergency department within six hours after the trauma. Dura-

tion of post-traumatic amnesia (PTA) and presence of transient loss of consciousness (LOC) were estimated on the basis of information from the patient and/or witnesses. MTBI was defined as a blunt blow to the head resulting in 1) PTA of less than 1 hour and/or 2) initial LOC of less than 15 minutes; 3) a Glasgow Coma Score of 14 or 15 on presentation at the emergency department and 4) absence of focal neurological signs. Patients were excluded if they suffered from multiple trauma or if they needed clinical observation. Patients with a history of traumatic brain injury, alcohol abuse or a psychiatric disorder were also excluded.

Outcome variables. The primary outcome variables were generic health status after two weeks, three months and six months. These were measured by means of the Medical Outcome Study 36-Item Short-Form Health Survey, which is recognized as a standard generic measure of physical and mental components of health status.(12) Based on a multidimensional model of health, the SF-36 is a multi-item self-rating scale that assesses eight health concepts, with a single question addressing change in health status. The eight health concepts can be divided into a physical, a mental and a mixed health dimension *(table 1)*.(12) The present study used the Dutch language version of the SF-36.(13).

The selection of PTC was based on an earlier study, which showed that these complaints differed in severity from those in control subjects. (7) They were measured on visual analog scales (VAS). At first follow-up, two weeks after the trauma, patients were also asked about the severity of these complaints before the trauma.

Study design. If patients met all admissibility criteria, written and oral explanations about the trial were given by the attending neurologist. A consent form was signed by both patient and physician before the patient was enrolled. Gender and age of the patient and cause of the accident were recorded at first examination. At discharge from the emergency department, the routine home observation instructions (to detect possible intracranial complications in the first 24 hours following the injury) were given to an accompanying person. At the follow-up visits to the outpatient clinic, patients' educational level was recorded and patients filled in questionnaires assessing the outcome variables.

Data analysis. Baseline data including age and gender and causes of injury were described. Raw scores on the SF-36 were transformed to scaled scores ranging from 0 to 100, with higher scores reflecting better health or less impact on functioning. Scores on the eight dimensions of the SF-36 were subdivided into a

Table 1. The 36-item Short-Form Health Survey Questionnaire (SF-36).

Health concept	Items, n	Dimension
Physical functioning	10	Physical
Role functioning-physical	4	Physical
Bodily pain	2	Physical
Role functioning-emotional	3	Mental
Mental health	5	Mental
Social functioning	2	Mixed
Vitality	4	Mixed
General health perception	5	Mixed

Table 2. Baseline data including demographics and cause of accident.

Factors known at first presentation after MTBI (n = 103)	
Individual factors	
Gender	
Female	43%
Age in years	
(mean 37.2; 15-75)	
15-25	28%
26-35	20%
36-45	20%
46-55	16%
56-65	9%
> 65	7%
Education	
Low	35%
Middle	34%
High	25%
Special or unknown	6%
Cause of accident	
Traffic	49%
In/around the house	18%
Work	12%
Sports	9%
Assault	9%
Other	3%

physical dimension ('Physical functioning', 'Role-functioning physical' and 'Bodily pain') and a mental dimension ('Mental health' and 'Role-functioning emotional'). The 'Social functioning', 'Vitality' and 'General health perception' sub-scores were classified as mixed dimension. The mean SF-36 sub-scores two weeks after the trauma were described. The means of the SF-36 sub-scores after three months were compared with the scores after two weeks, using the T-test for paired samples. The same was done for the scores at six months compared to those at three months. Medians and 5 and 95 percentiles of VAS scores for all PTC after six months were recorded. Patients were divided into a group 'with PTC' and a group 'without PTC' after six months. Patients were considered to be 'without PTC' if the VAS scores of all PTC after six months were lower than the 95 percentile of the pre-traumatic VAS scores retrospectively measured at the first follow-up moment. If one or more VAS scores after six months were higher than the pre-traumatic 95 percentile, the outcome was defined as 'with PTC'. The mean SF-36 sub-scores at six months in the 'without PTC' and 'with PTC' groups were compared using non-parametric Mann-Whitney U tests.

RESULTS

Between October 1996 and June 1999, 107 MTBI patients were enrolled in the study. After two weeks, 103 patients showed up for follow-up examination (96%), versus 86 (80%) after three months and 79 (74%) after six months. Baseline variables were described for the 103 patients showing up after two weeks *(table 2)*. The SF-36 sub-scores in the course of six months after the trauma, divided into 'physical', 'mental' and 'mixed' dimensions, are shown in *fig. 1*. Improvements in sub-scores of physical dimensions were statistically significant between two weeks and three months, while sub-scores of mental dimensions did not alter much between these follow-up moments *(table 3)*. In contrast, the improvement in the mental sub-score of 'Role-functioning emotional' between three and six months was statistically significant. Although statistically significant, 'Role-functioning physical' and 'Social-functioning' improved less between three and six months than between two weeks and three months. 'General health perception' not change in the course of six months.

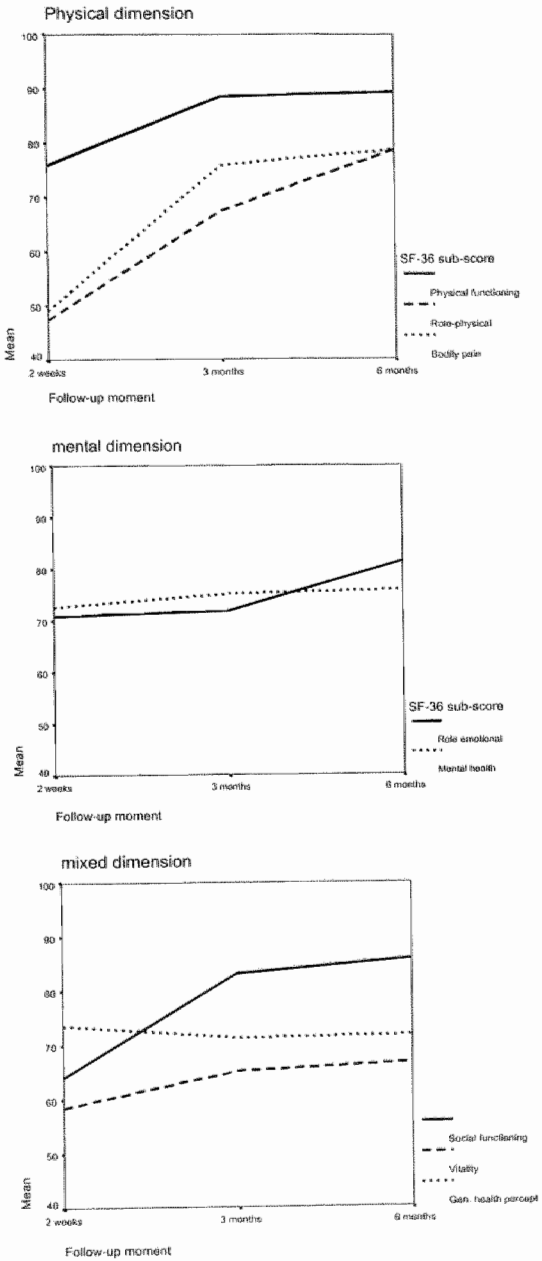

Fig 1. SF-36 sub-scores in the course of six months after a mild traumatic brain injury.

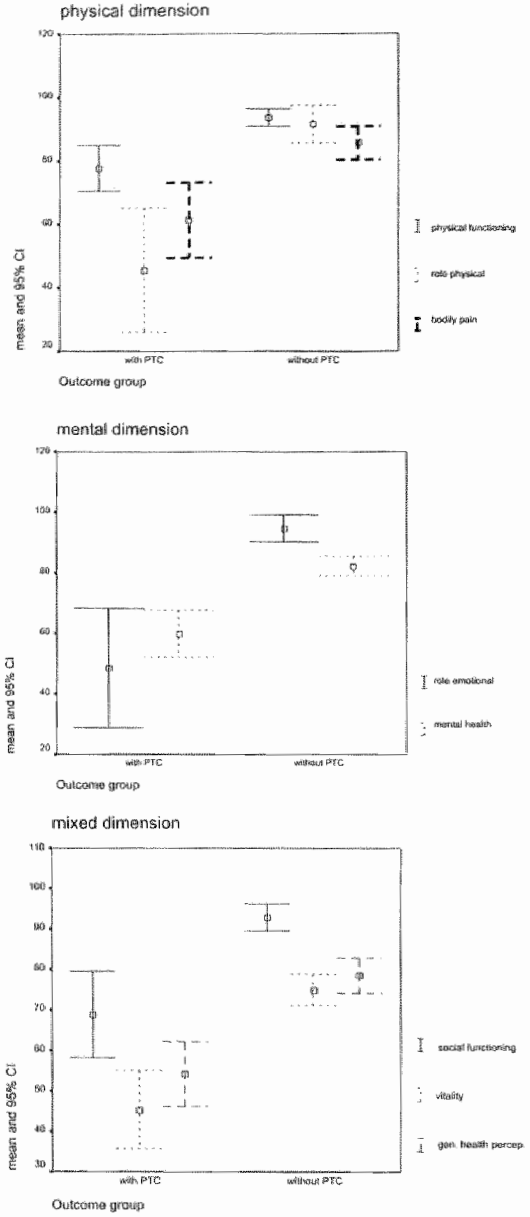

Fig 2. SF-36 sub-scores six months after a mild traumatic brain injury in patients with and without post-traumatic complaints.

Table 3. SF-36 sub-scores at three different follow-up moments after a mild traumatic brain injury.

SF-36 scores* (mean)	Follow-up moment		
	2 weeks (n=103) T1	3 months (n=86) T2 –T1 (95% CI)§	6 months (n=79) T3–T2 (95% CI)§
Physical functioning	76	**14 (10–16)**	1 (-2– 4)
Role (physical)	47	**23 (11–34)**	**13 (5–20)**
Bodily pain	49	**28 (22–34)**	5 (0– 9)
Role (emotional)	76	2 (-7–11)	**12 (4–20)**
Mental health	73	2 (-2– 7)	2 (-1– 5)
Social functioning	64	**21 (14–27)**	**4 (1– 7)**
Vitality	59	**8 (3–13)**	2 (-1– 5)
General health	74	-2 (-6– 2)	1 (-3– 4)

* Raw scores on the SF-36 were transformed to scaled scores ranging from 0 to 100, with higher scores reflecting better health or less impact on functioning.
§ = mean increase (95% Confidence Intervals) in SF36 sub-scores in comparison with scores at previous follow-up (paired sample T-test).

VAS-scores of PTC after six months and pre-traumatic VAS-scores are summarised in *table 4*. Twenty-two of 79 patients (28%) were classified as 'with PTC' after six months. SF-36 sub-scores in patients with and without PTC after six months are presented in *fig2*. All mean SF-36 sub-scores in patients with PTC were significantly higher than in those without PTC (Mann Whitney U; $p < 0.0001$)

Table 4. Severity of post-traumatic complaints six months after a mild traumatic brain injury.

VAS ‡ score of post-traumatic complaints	Follow-up moment	
	Before trauma* median (5-95percentile)	Six months (n=79) median (5-95 percentile)
Trouble concentrating	0 (0-50)	1 (0-80)
Easily overwhelmed by problems	0 (0-45)	0 (0-66)
Forgetful	1 (0-45)	1 (0-70)
Flushing easily	0 (0-53)	0 (0-20)
Feeling short of breath	0 (0-55)	0 (0-52)
Feeling faint	0 (0-59)	0 (0-53)
Depressed	0 (0-48)	1 (0-59)
Drowsy	0 (0-43)	3 (0-90)
Crying more easily	0 (0-41)	0 (0-19)
Confused	0 (0-22)	0 (0-49)
Headache	1 (0-59)	3 (0-75)
Dizziness	0 (0-32)	3 (0-60)
Nausea	0 (0-14)	0 (0-26)
Light-headed	0 (0-33)	1 (0-60)
Paresthesia of arm(s)	0 (0-29)	1 (0-62)
Sleeping problems	1 (0-83)	0 (0-57)

‡ VAS = visual analogue scale.
* measured retrospectively at first follow-up.

DISCUSSION

The present study is the first in which generic health status was followed over a period of six months after MTBI using the SF-36 Health Survey Questionnaire. Our results confirm Paniaks' finding that generic health status is impaired after MTBI and that physical health dimensions and social functioning are more affected than mental health dimensions. The physical health dimension improved mainly between two weeks and three months, whereas improvement of the mental health dimension chiefly occurred between three and six months after the trauma. Because no non-trauma reference group was used in the present study, the results of our study do not show directly whether generic health status is still

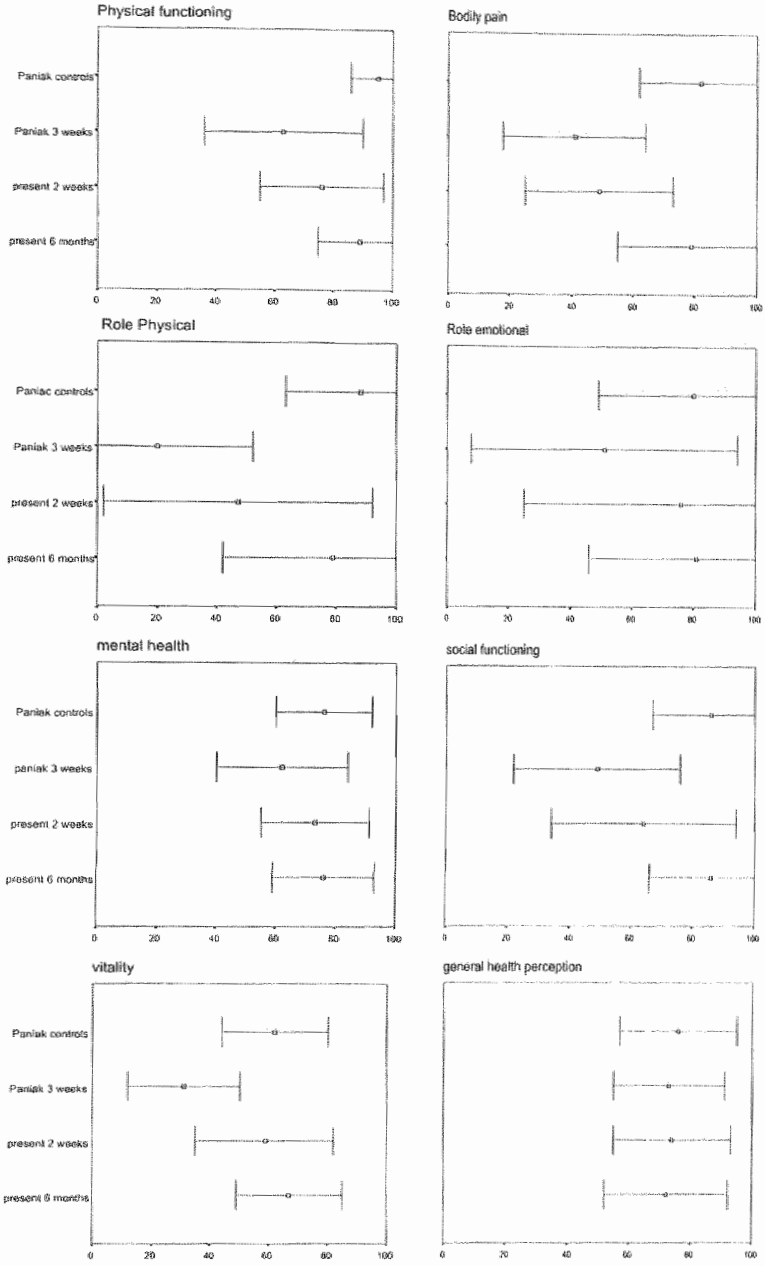

Fig 3. SF-36 sub-scores at various follow-up moments in Paniaks'study and our study.

affected six months after the trauma. However, six months after the trauma, patients in the present study had scores similar to those of the healthy controls in Paniaks' study on all SF-36 dimensions *(fig 3).*(11) Apart from 120 healthy subjects, Paniak evaluated SF-36 scores in 120 patients, three weeks after MTBI (GCS 13-15 and PTA <24 hours). In our study, patients scored slightly better on all SF-36 sub-scores two weeks after the trauma than the patients in Paniaks' study did three weeks after MTBI *(fig3).* This difference could be the result of the stricter MTBI definition used in our study (PTA < 1 hour). The scores on the sub-item 'General health perception' after two weeks and six months in the present study were similar to scores found by Paniak et al. in controls and in MTBI patients after three weeks. This finding confirms Paniaks' finding that even shortly after injury most MTBI patients reported good overall health. However, we also found that the small group of patients with PTCs six months after the trauma had poorer scores for 'General health perception', and all other SF-36 sub-items, than patients without PTC.

We conclude that most MTBI patients have a normal generic health status after six months. However, patients with PTC after six months have a clearly impaired generic health status at that moment. The 36-item Short Form Health Survey Questionnaire SF-36 seems a useful additional test to estimate the influence of MTBI on daily life activities for clinical trials evaluating outcome after MTBI.

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CHAPTER 8

EFFECTIVENESS OF BED REST AFTER MILD TRAUMATIC BRAIN INJURY

A randomised trial of none versus six days of bed rest

Presented at the 53rd annual meeting of the American Academy of Neurology; 2001; Philadelphia, USA

Adapted from:
Kruijk de J, Leffers P, Meerhoff S, Rutten J, Twijnstra A. Efficacy of Bed rest after Mild traumatic Brain Injury: a randomized trial of none versus six days of bed rest. *Submitted*

ABSTRACT

Background: Mild traumatic brain injury (MTBI) accounts for most cases of traumatic brain injury and outcome is largely determined by the appearance of post-traumatic complaints (PTC). The prevalence of PTC after six months is estimated to be between 20 and 80%. Bed rest has been advocated to prevent PTC, but its effectiveness has never been established. The aim of the present study was to evaluate the effect of bed rest on the severity of PTC after MTBI.

Methods: Patients presenting with MTBI at the emergency room were randomised over two intervention strategies. One group was advised not to take bed rest (NO), the other to take full bed rest (FULL) for six days after the trauma. The primary outcome measures were severity of post-traumatic complaints on a visual analogue scale, and physical health and mental health on the MOS 36-item short-form health survey (SF-36) at two weeks and three and six months after the trauma.

Results: Between October 1996 and July 1999, 107 (54 NO, 53 FULL) patients were included. Outcome variables in both groups clearly improved between two weeks and six months. After adjustment for differences in baseline variables, most PTC tended to be somewhat more severe in the FULL group six months after the trauma but no statistically significant differences were found. Neither were there any statistically significant differences in the outcome parameters between the two groups after three months. Two weeks after the trauma, most PTC in the FULL group were slightly less severe than in the NO group and physical sub-scores of the SF-36 in the FULL group were slightly better. These differences were not statistically significant. Patients in the FULL group reported significantly less severe dizziness during the intervention period.

Conclusions: As a means of speeding up recovery of patients with PTC after MTBI, bed rest is no more effective than no bed rest at all. Bed rest probably has some palliative effect within the first two weeks after the trauma.

INTRODUCTION

Mild traumatic brain injury (MTBI) accounts for about 90% of all traumatic brain injuries.(1-3) In addition to the individual impairments, the burden to society is also large, in terms of hospital costs and production loss resulting from post-traumatic complaints (PTC).
(4, 5)
Apart from very rare acute intracranial complications, outcome after MTBI is mostly determined by the appearance of PTC. Although the severity of most PTC declines during the first three months,(6, 7) the prevalence of PTC after six months is estimated at 20- 80%.(8-11) The huge variation in these estimates probably mainly reflects the different definitions of MTBI and PTC used in the various studies. In addition to PTC, both brain and non-brain (eg, musculoskeletal) injuries in MTBI patients negatively affect generic health status during the first year after the trauma.(12)
Education, rehabilitation and drugs have been used with at best limited success in the prevention and treatment of PTC.(5, 13-19) The effectiveness of bed rest for preventing PTC has hardly been studied, with only one study seeming to suggest that longer bed rest leads to an increase in PTC.(20) Notwithstanding this uncertainty about the efficacy of bed rest, many European neurologists (40%) continue to recommend one or more days of full bed rest after MTBI.(21) Doubt has been cast on the effectiveness of bed rest in many situations where it has traditionally been recommended. A recent review of randomised trials on bed rest for 15 other medical conditions concluded that bed rest did not improve the prognosis (for example in uncomplicated myocardial infarction) or even worsened the outcome in some situations (for example in spontaneous labour).(22) We conducted a randomised trial of the effectiveness of six days of bed rest versus no bed rest in terms of the severity of PTC and generic health status after six months.

METHODS

Participants. The study was approved by the institutional ethics committee of the Maastricht University Hospital and all patients provided written informed consent.

Patients were eligible for this study if they were older than fifteen years and presented at the emergency department within six hours after the trauma. Duration of post-traumatic amnesia (PTA) and presence of transient loss of consciousness (LOC) were estimated on the basis of information from the patient and/or witnesses. MTBI was defined as a blunt blow to the head resulting in 1) PTA of less than 1 hour and/or 2) initial LOC of less than 15 minutes; 3) a Glasgow Coma Score of 14 or 15 on presentation at the emergency department and 4) absence of focal neurological signs. Patients were excluded if they suffered from multi-trauma or when there was necessity for clinical observation. Patients with a history of traumatic brain injury, alcohol abuse or psychiatric disorder were also excluded.

Intervention. The difference between the strategies compared was the amount of recommended bed rest between 8.00 AM and 8.00 PM during the first week after the trauma. Patients in the no bed rest group (NO) were instructed to mobilise from the first day after the trauma, with at most four hours of bed rest on the first day, three hours on the second day, two hours on the third day and one hour on the fourth day. Patients were expected to resume normal daily activities and/or work on the fifth day. Patients in the full bed rest group (FULL) were instructed to take full bed rest during the first six days following the trauma. Starting from day 7, patients were advised to follow the same mobilisation schedule given to the NO group. The maximum number of hours of bed rest in the NO group was to be 10, while the patients in the FULL group were expected to rest for between 72 hours and 82 hours.

Outcome variables. The primary outcome variables were the severity of sixteen PTC and generic health status at two weeks, three months and six months after the trauma. The PTC, which were measured on a visual analog scale (VAS), were divided into four subgroups (cognitive, dysthymic, vegetative, and physical) in accordance with an earlier study.(10) Generic health status was measured by means of the MOS 36-item short-form health survey (SF-36); Dutch language version (23) which is recognized as a standard generic measure of physical and mental components of health status.(24)

Study design. If patients fulfilled all admissibility criteria, written and oral explanations about the trial were given by the attending physician (neurology resident). A consent form was signed by the patient and the physician before the patient was enrolled. In order to obtain equal group sizes, randomisation was

done in blocks of 2 and 4. The sequence of block sizes was determined at random.

The gender and age of the patient, the cause of the accident and the presence of headache, nausea, vomiting and dizziness were recorded at first examination. Traumatic injuries to limbs, trunk or head were also recorded and if necessary, radiological examination was performed. The assigned advice was explained by the physician and it was also clearly summarised on the first page of the medical diary that each patient received. To evaluate their compliance, patients were asked to note the daily number of hours of bed rest during the first 10 days following the trauma. This diary also contained questions about the use of analgesics and recorded the severity of headache, dizziness and nausea by means of a VAS. Another VAS was used to let patients score the level of difficulty they experienced in complying with the advice during a particular day. At discharge from the emergency department, the routine home observation instructions (to detect possible intracranial complications in the first 24 hours following the injury) were given to an accompanying person. At the follow-up visits to the outpatient clinic, patients filled in questionnaires assessing the outcome variables.

Analysis. Baseline data including age and gender, causes and symptoms of injury were compared between the NO and FULL groups. The total duration of bed rest during the first ten days, the sum of the levels of difficulty experienced in complying with the assigned advice over the first four days and the number of analgesics tablets used over the first four days were calculated and compared between the two groups. The same was done for headache, dizziness and nausea during the first four days of intervention. Raw scores on the SF-36 were transformed to scaled scores ranging from 0 to 100, with higher scores reflecting better health or less impact on functioning. The median VAS scores of the 16 PTC and the mean SF-36 scores for the various follow-up moments were compared between the NO and FULL groups. Since some of the baseline parameters differed between the two groups, differences in outcome between the two intervention groups were tested by means of multiple linear regression analysis of ln VAS scores of post-traumatic complaints and SF-36 scores on gender, social situation and the presence of headache, dizziness and vomiting at the ER.

RESULTS

Between October 1996 and June 1999, approximately 1125 patients with MTBI were seen at the University Hospital of Maastricht.(3) One hundred and seven of these patients were enrolled in the study. The rest met the exclusion criteria, refused to be included, or were not asked by the attending specialist to partici-

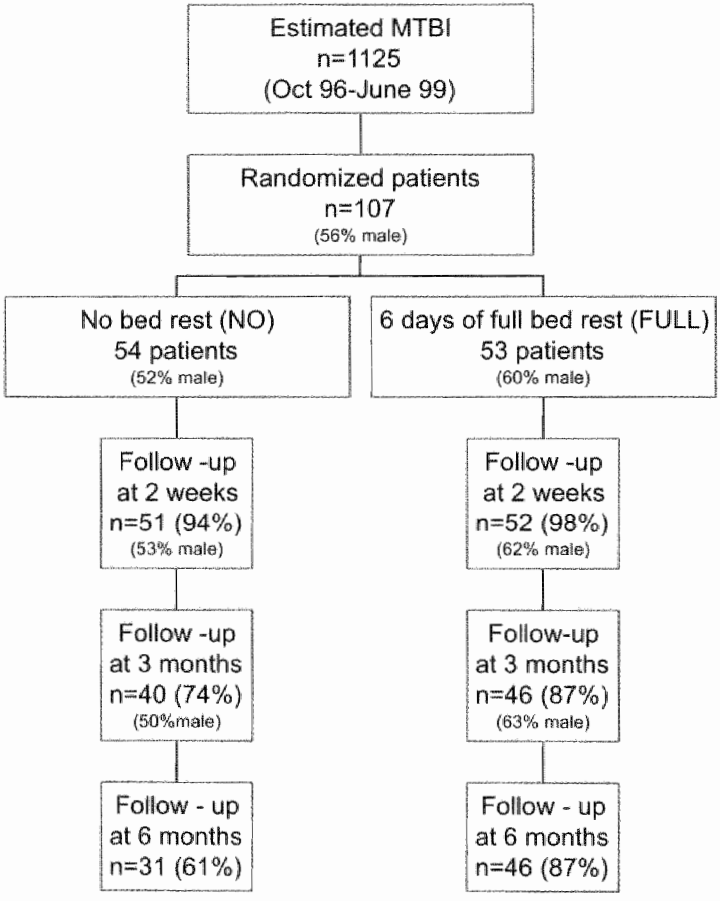

Fig 1. Trial profile.

pate. Ultimately, 54 patients received the NO bed rest advice, while 53 received the FULL bed rest advice. *Figure 1* shows the flow of the patients in the trial. Four patients were lost to follow-up and nine patients did not fill in their medical diaries during the intervention. After two weeks, 95% of patients from the NO group and 98% of those from the FULL group were examined and interviewed. After three months and six months, more patients in the FULL group showed up for follow-up (87% on both occasions) than in the NO group (74% and 61%, respectively). The intervention groups were similar with regard to the distributions of age, educational level, cause of the accident, occurrence of LOC and duration of PTA *(table 1)*. The FULL group had relatively more male patients than the NO group (60% vs 52%) and fewer patients living alone (36% vs 50%). Patients in the FULL group reported some more headache and dizziness in the emergency room before they were randomised, whereas patients included in the NO group vomited more.

Intervention. The mean duration of bed rest in the NO group was 26 hours. After the exclusion of two women who reported 260 and 158 hours of bed rest, the mean for this group became 17 hours *(Table 2A)*. Patients in the FULL group rested for an average of 57 hours during the first ten days after the trauma. Patients in the FULL group found it more difficult to comply with the advice during the first four days of intervention than those in the NO group *(Table 2A)*, but this difference was not statistically significant ($p=0.47$; Mann Whitney U). Patients in the FULL group used more oral analgesics (median: 3) than those in the NO group (median: 1) *(table 2A)*. This difference was not significant either ($p=0.47$; Mann Whitney U).

During the first four days of the intervention, patients in the FULL group suffered significantly less dizziness than in the NO group *(table 2B)*. Headache and nausea were also reported slightly (not significantly) less severe in the FULL group after adjustment for differences in baseline variables.

Follow-up. In both intervention groups, severity of PTC diminished and SF-36 scores improved between two weeks and six months after the trauma *(tables 3 and 4)*. After six months, patients in the FULL group reported slightly higher VAS scores on 12 of the 16 PTC after adjustment for baseline differences *(table 3 and fig 2)*. Only 'headache', 'flushing easily', 'being easily overwhelmed by problems' and 'having trouble concentrating' scored somewhat lower. Apart from 'flushing easily', none of the differences were statistically significant. Given the fact that the

Table 1. Patient characteristics.

	NO (n=54)	FULL (n=53)
Gender		
Male	52%	60%
Age in years		
Mean (SD)	39.9 (14.5)	34.1 (16.5)
Range	15-72	17-76
Education		
Low level	30%	32%
Medium level	31%	42%
Higher / University level	24%	19%
Special	7%	4%
Unknown	7%	4%
Social situation		
Living alone	52%	38%
Married	35%	51%
Living with other person(s)	6%	8%
Other	7%	3%
Cause of accident		
Traffic	43%	53%
Work	17%	19%
In or around the house	13%	9%
Sports	13%	6%
Violence	9%	8%
Unknown / Other	6%	6%
Reported symptoms on ER		
LOC	80%	77%
PTA in minutes		
mean (SD)	19 (17)	19 (19)
Headache	54%	70%
Dizziness	13%	21%
Nausea	30%	25%
Vomiting	11%	2%

LOC = Loss of consciousness.
PTA = Post-traumatic amnesia.

Table 2A. Intervention characteristics of the two groups.

	NO	FULL	
Hours of bed rest Mean (min-max) during days 1-10	26 (0-261) 17 (0-72)*	57 (14-102)	
Difficult to comply with advice [#] Median (5 and 95 percentiles);	71.0 (0-391)	118 (0-363)	p=0.47 Mann-Whitney U
Number of oral analgesic tablets[#] Median (5 and 95 percentiles);	1 (0-24)	3 (0-17)	p=0.47 Mann-Whitney U

*Two patients with extreme bed rest duration (260 and 158 hours) were excluded.
# sum day 1-4.
NO = no bed rest.
FULL = 6 days bed rest.

Table 2B. Symptoms during intervention in the two groups.

	NO	FULL	FULL versus NO
Symptoms during intervention	Median (5 and 95 percentiles)	Median (5 and 95 percentiles)	Exp B* (95% CI)[§]
Headache[#]	93 (0-364)	95 (0-341)	0.87 (0.42-1.80)
Dizziness[#]	49 (0-297)	28 (0-296)	**0.41 (0.17-0.88)**
Nausea[#]	13 (0-296)	14 (0-201)	0.78 (0.33-1.86)

*b = Coefficients from linear regression analysis of ln outcome variable (symptoms during intervention) on intervention (FULL versus NO bed rest) after adjustment on gender, social situation and headache, dizziness and vomiting in the ER.
Sum of visual analogue scales (VAS) for days 1-4.
§ 95% Confidence interval for exp B.
NO = no bed rest.
FULL = 6 days bed rest.

medians for 'flushing easily' were zero in both groups, the difference, though statistically significant, was small. After six months, no statistically significant differences in SF-36 scores were found between the two groups, though patients in the FULL group had slightly poorer scores on the bodily pain sub-scale of the SF-36 after adjustment for baseline differences *(table 4 and fig 3)*.

Table 3. Post-traumatic complaints during follow-up.

Post-traumatic complaints[#]	2 weeks Median (5-95 percentiles)		3 months Median (5-95 percentiles)		6 months Median (5-95 percentiles)	
	NO (n=51)	FULL (n=52)	NO (n=40)	FULL (n=46)	NO (n=31)	FULL (n=46)
Cognitive PTC						
Trouble concentrating	6 (0-96)	7 (0-89)	2 (0-84)	2 (0-63)	1 (0-55)	1 (0-85)
Easily overwhelmed by problems	0 (0-50)	0 (0-10)	0 (0-81)	1 (0-31)	0 (0-46)	1 (0-67)
Forgetful	7 (0-61)	13 (21)	4 (0-82)	5 (0-62)	1 (0-30)	4 (0-83)
Vegetative						
Flushing easily	0 (0-21)	0 (0-31)	0 (0-32)	1 (0-40)	0 (0-22)	0 (0-15)
Feeling short of breath	0 (0-65)	0 (0-50)	0 (0-85)	1 (0-80)	0 (0-37)	1 (0-58)
Feeling faint	0 (0-77)	0 (0-29)	0 (0-48)	0 (0-40)	0 (0-18)	1 (0-61)
Dysthymic						
Depressed	1 (0-61)	0 (0-49)	1 (0-88)	2 (0-54)	0 (0-35)	1 (0-62)
Drowsy	23 (0-91)	8 (0-95)	3 (0-85)	2 (0-75)	2 (0-72)	3 (0-91)
Crying more easily	0 (0-55)	0 (0-49)	0 (0-88)	1 (0-41)	0 (0-17)	1 (0-42)
Confused	1 (0-54)	0 (0-72)	0 (0-79)	1 (0-60)	0 (0-29)	1 (0-71)
Physical						
Headache	17(0-100)	9 (0-94)	0 (0-50)	4 (0-69)	4 (0-29)	3 (0-83)
Dizziness	15 (0-90)	11 (0-96)	0 (0-58)	3 (0-77)	1 (0-42)	4 (0-72)
Nausea	0 (0-68)	0 (0-43)	0 (0-26)	1 (0-76)	0 (0-19)	0 (0-57)
Light-headed	3 (0-61)	3 (0-57)	0 (0-48)	2 (0-49)	1 (0-19)	1 (0-67)
Paraesthesia of arm(s)	0 (0-67)	0 (0-36)	0 (0-46)	1 (0-73)	0 (0-24)	1 (0-68)
Sleeping problems	1 (0-88)	0 (0-80)	0 (0-76)	1 (0-94)	0 (0-57)	1 (0-70)

# measured on visual analogue scale (VAS).
NO = no bed rest.
FULL = 6 days bed rest.

Table 4. Physical and mental health during follow-up.

SF-36#	2 weeks Mean (SD)		3 months Mean (SD)		6 months Mean (SD)	
	NO (n=51)	FULL (n=52)	NO (n=40)	FULL (n=46)	NO (n=31)	FULL (n=46)
Physical functioning	76 (22)	76 (21)	87 (17)	90(14)	91 (12)	88 (15)
Role functioning						
physical	41 (44)	54 (45)	60 (43)	75 (40)	81 (35)	77 (38)
emotional	74 (41)	68 (42)	72 (38)	71 (39)	83 (32)	80 (37)
Social functioning	65 (30)	63 (31)	83 (21)	84 (19)	86 (19)	86 (21)
Bodily pain	53 (23)	44 (23)	74 (23)	78 (25)	84 (19)	74 (27)
Mental health	74 (19)	71 (17)	75 (18)	76 (18)	76 (17)	75 (19)
Vitality	57 (23)	60 (23)	65 (20)	65 (22)	66 (18)	68 (24)
General health perception	75 (21)	72 (16)	71 (21)	72 (16)	74 (19)	70 (20)

# Raw scores on the SF-36 were transformed to scaled scores ranging from 0 to 100, where higher scores reflect better health or less impact on functioning.
NO = no bed rest.
FULL = 6 days bed rest.

After three months, most PTC in the 'physical' category were given slightly higher scores in the FULL group, whereas cognitive and dysthymic complaints tended to be given slightly lower scores in this group *(fig 2)*. Patients in the FULL group had slightly better scores on almost all SF-36 sub-scales *(table 4)*. Only the difference for physical role functioning was more marked. None of these differences were significantly different after three months.

After two weeks, patients in the FULL group had slightly lower VAS scores than those in the NO group on 14 of the 16 PTC *(fig 2)*. The only significant difference, however, was in 'feeling faint', but since the medians for both groups were zero, the group difference was very small. 'Forgetfulness' and 'crying more easily' were given higher scores in the FULL group after two weeks. At this same follow-up moment, patients in the FULL group had higher scores on the SF-36 sub-scales of physical role (p=0.09) and vitality, both measuring physical health *(table 4 and fig 3)*. However, these patients scored slightly lower on emotional role functioning and also had more bodily pain than those in the NO group. Again, none of the differences reached statistical significance.

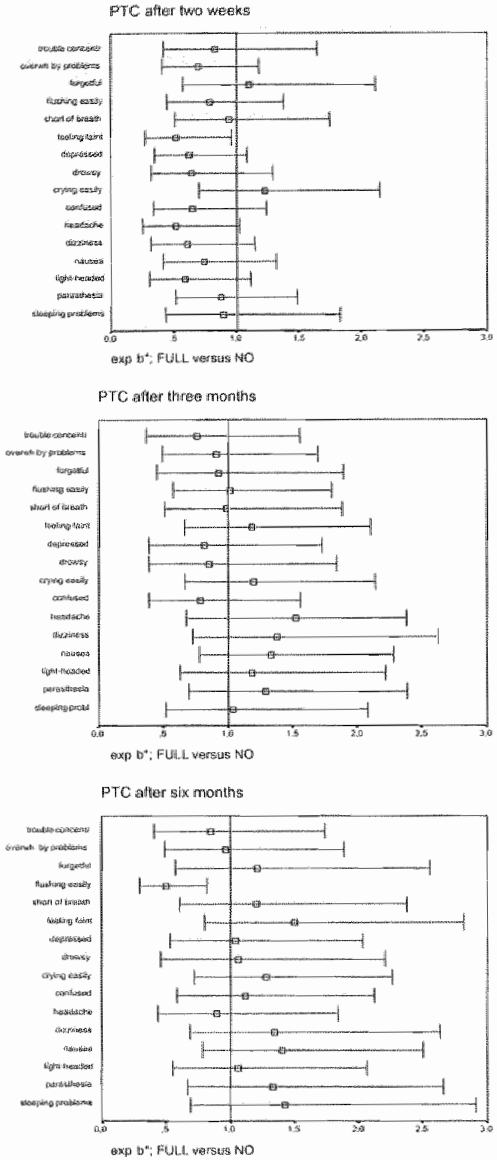

Fig 2. Post-traumatic complaints after 2 weeks, 3 months and 6 months in mild traumatic brain injury patients with and without full bed rest.

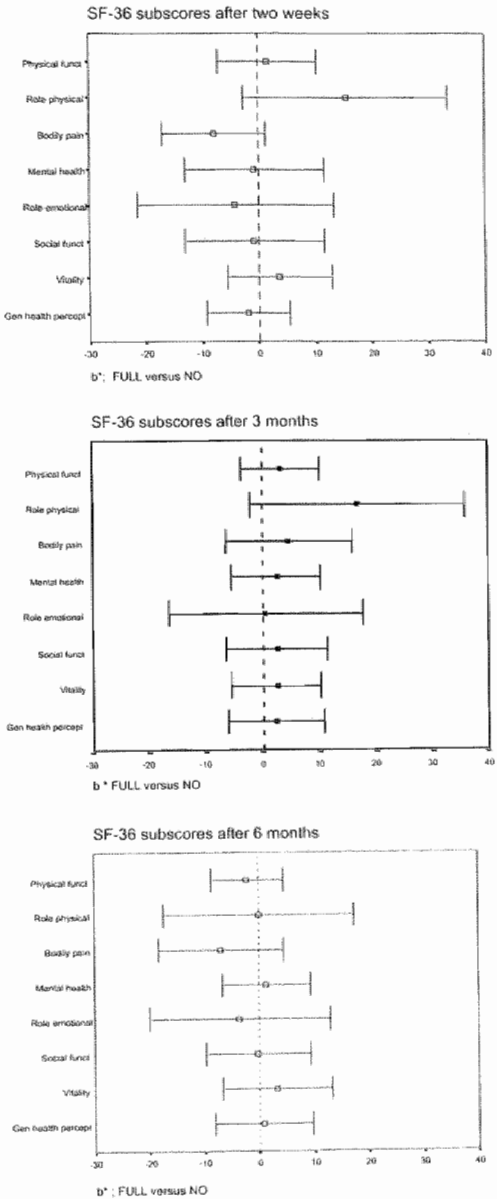

Fig 3. SF-36 sub-cores after 2 weeks, 3 months and 6 months in mild traumatic brain injury patients with and without 6 days full bed rest.

DISCUSSION

Principal findings. The results of the present study indicate that the advice to take six days of complete bed rest had no beneficial effect on the severity of PTC or on generic health status at six months after MTBI.

Relation to other studies. Previous studies have addressed both the effectiveness of PTC prevention and the treatment of persistent PTC in patients with MTBI. However, an generally accepted treatment of MTBI patients to prevent PTC has never been established. Educating patients about possible complications shortly after MTBI might help to reduce the severity of PTC later on.(5, 13, 15, 16) Pharmacological treatment seems to have little or no effect on either prevention or treatment of PTC.(17-19, 25) The effectiveness of bed rest in patients with MTBI has never before been investigated in a randomised trial, though one study suggested that bed rest lasting more than two weeks after MTBI resulted in poorer outcome than briefer bed rest.(20) Because this was an observational study, no conclusion about causality could be drawn. Indeed, the same association would have been found if greater severity of the trauma led to both longer bed rest and more PTC.

In a recent survey in Europe, we found that many neurologists (40%) recommend full bed rest after MTBI. The recommended period of bed rest ranged from 1-14 days (21) The study concluded that there was no consensus about recommendations for the length of bed rest, the length of the work pause and the need for any follow-up of these patients.

Strengths and weaknesses of the present study. Estimated prevalence and severity of PTC in previous studies have often differed because different definitions of MTBI were used. The MTBI patient population in the present study was clearly defined according to the most recent opinion in literature.(7, 26, 27)

In order to evaluate compliance with the prescribed bed rest, we measured the actual duration of bed rest in both groups. Although patients in the NO group rested for too long (a mean of 7 hours too long) and patients in the FULL group rested for less than the recommended number of hours (a mean of 15 hours less), a robust contrast between the intervention groups was obtained.

The number of patients included in our study was lower than expected, given the large number of MTBI patients presenting at our hospital during the inclusion period. Since the rate of non-inclusion was mostly caused by work strain in the

emergency department, it seems unlikely that the enrolled patients represented a selection of patients for whom bed rest was less or more effective. A larger study would have been more attractive, but in our opinion, the present results support the conclusion that bed rest does not improve outcome at six months after mild traumatic brain injury. The null-hypothesis: "Bed rest after mild traumatic brain injury does not improve outcome at six months" could not be rejected statistically. However, it is very unlikely that a larger sample size would show a favourable effect of bed rest because at 6 months follow up, for most outcome variables there was a trend that favoured the no bed rest group.

The follow-up rates of 87% (FULL) and 61% (NO) at six months were similar to those in earlier studies.(16, 28) Our evaluation was made at the outpatient clinic, and it proved impossible to achieve complete follow-up in this group of relatively young, working and often fully recovered patients. Although we do not know the reasons why fewer patients showed up in the NO group, we found that most patients who did not show up after six months had no complaints at three months. This finding supports the idea that the absence of PTC was a reason for not showing up for follow-up in the whole group, but that patients in the FULL group may have been more motivated to show up for follow-up due to their more intensive treatment. If this is true, the severity of PTC in both groups was overestimated and this bias would be larger in the NO group than in the FULL group. As a consequence, the negative effect of bed rest at six months should have been even more pronounced.

Implications for MTBI patients. In spite of the fact that our results do not show a clear effect of bed rest on outcome after MTBI, some notable trends became apparent from this study:

First, during the first days following a MTBI, patients who were advised to take full bed rest reported significantly less dizziness than patients who were advised not to take bed rest. However, patients in the full bed rest group found it more difficult to comply with the advice to take bed rest, and used more oral analgesics.

Second, almost all post-traumatic complaints after two weeks tended to be less severe in the FULL group, while after six months, there were hardly any differences. It was especially the 'physical' complaints which seemed to be favourably influenced by bed rest in the short term, while this positive effect of bed rest completely disappeared or was even reversed later.

Third, bed rest also had a slight positive effect on physical health as measured by the SF-36 after two weeks, but this positive effect may have been offset by the increased experience of bodily pain and the slightly worse mental health shortly after the intervention period.
In view of these findings, bed rest probably can palliate dizziness during the first week after the trauma. We do not recommend bed rest to improve outcome after mild traumatic brain injury.

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CHAPTER 9

SUMMARY AND CONCLUSIONS

Although traumatic brain injury is an important cause of morbidity and mortality, most cases are classified as mild traumatic brain injury (MTBI). Outcome after MTBI is mainly determined by the severity and persistence of post-traumatic complaints (PTC) like headache, dizziness, poor concentration and depression. Although the severity of most PTC declines during the first three months, their prevalence of PTC six months after the trauma is still appreciable. Predicting the severity of PTC and trying to prevent these complaints is important because they can lead to high costs of health care and to loss of labour productivity work days. Damage to the brain in MTBI patients has been demonstrated by means of elevated serum marker concentrations and abnormalities on Magnetic Resonance Imaging of the brain. However, it is not clear whether PTC are directly caused by brain injury or are rather the result of the trauma experience in combination with psychosomatic, emotional or motivational factors.

In this thesis several studies are presented intending to improve our understanding of the consequences of MTBI for patients.
The first part of the thesis discusses some general topics regarding MTBI. Initially, a literature review of the definitions, diagnostics and treatment used for MTBI was performed. In addition, the frequency of traumatic head and brain injury was estimated by measuring the incidence in a well-defined catchment area in the Netherlands. We also sent questionnaires to neurologists in several European hospitals asking what guidelines they used in their management of MTBI patients.
The second part of the thesis describes follow-up results of a group of MTBI patients from the moment they presented at the emergency room until six months after the trauma. The biochemical serum markers S-100B and Neuron-Specific Enolase(NSE) in the serum of MTBI patients in the acute situation were measured. Additionally, the olfactory function in MTBI patients after two weeks was also measured.
Outcome in MTBI patients was studied in the course of six months after the trauma. During the first days, MTBI patients often show symptoms like headache, neck pain, nausea, dizziness and vomiting. Like biochemical markers, these acute clinical symptoms could be helpful in assessing the severity of the brain damage. They might also be useful in predicting the occurrence of PTC after MTBI. We assessed the association of serum marker concentrations and the pres-

ence of acute symptoms at the emergency room with the severity of PTC six months after the MTBI.
Educating MTBI patients shortly after the accident about possible complications might help to reduce the severity of PTC. In order to determine which MTBI patients require follow-up at the outpatient clinic, we investigated which combination of acute symptoms and serum markers best predicted the presence of PTC after six months.
Bed rest has been found not to improve the prognosis, and even worsened the outcome in several other medical conditions but the effectiveness of bed rest in preventing PTC has hardly been studied. Still, almost half of the 100 Dutch neurologists surveyed recommended one or more days of bed rest after MTBI. To assess the usefulness of bed rest, we conducted a randomised trial on the effectiveness of six days of bed rest versus no bed rest on the outcome after six months.
Long-term consequences of MTBI for generic health status had not been investigated before. We therefore evaluated its effect on patients' generic health status after two weeks, three months and six months. We also investigated the association between generic health status and the presence of PTC after six months.

In **Chapter 1** we reviewed the definitions, differential diagnosis and management of MTBI. We concluded that traumatic brain injury should only be classified as mild if the Glasgow Coma Score (GCS) is optimal (EMV=15) within six hours of admission. Post-traumatic amnesia lasting less than one hour and loss of consciousness lasting less than fifteen minutes are suggested as additional diagnostic criteria. These findings were used in the definition of MTBI in the subsequent studies.

In **chapter 2** we measured the incidence of traumatic head and brain injury (THBI) in the catchment area of the University Hospital Maastricht in 1997. The incidence rate of THBI in 1997 was 836/100,000. The frequency of hospital admissions (88/100,000) was extremely low. Head injury without brain injury was diagnosed in 75%.The proportion of THBI patients with mild injuries (head injury and/or MTBI) was 99%. This figure was high compared to those reported by other studies. In the sub-group of patients with brain injury, 95% had MTBI, corresponding to an incidence of 201/100,000.

In **chapter 3** we described the management of MTBI patients in various European hospitals. A short questionnaire was sent to neurologists in several European countries. Almost all respondents (94%) reported that they admitted patients with MTBI to hospital for observation. Forty-one percent of respondents advised patients to take 1 to 14 days of bed rest. Taking sick leave from work was prescribed by 64%, ranging from 1 to 30 days. At least one follow-up visit was considered necessary by 70% of respondents. National guidelines were referred to by 43% of respondents. At present, according to the results, no consensus about criteria for, or management of MTBI in European hospitals.

In **Chapter 4** we measured serum concentrations of Neuron-Specific Enolase (NSE) and S100-B in MTBI patients and controls. Median NSE concentration was only slightly higher in patients (9.8 μg/l; 10 to 90 percentile range 6.9 to 14.3 μg/l) than in controls (9.4 μg/l; 6.3 to 13.3 μg/l). Median S-100B concentration was significantly higher in patients (0.25 μg/l; 0.00 to 0.68 μg/l) than in controls (0.02 μg/l; 0.00 to 0.13 μg/l). An association was found between S-100B concentrations and vomiting in patients. We concluded that S-100B is a potentially useful marker for brain damage in MTBI.

In **Chapter 5** we estimated the prevalence of quantitative olfactory dysfunction after MTBI. Associations of early symptoms and S-100B and NSE serum concentrations with threshold levels of olfactory functions two weeks after MTBI were also examined. The prevalence of olfactory dysfunction two weeks after MTBI was 26%. No associations were found between early symptoms, biochemical marker concentrations and olfactory threshold levels. This was surprising because the study reported in chapter 6 demonstrated acute MTBI parameters to be associated with other outcome variables. We concluded that MTBI is associated with post-traumatic olfactory dysfunction, but also that it is important to reproduce our findings and to check the validity of the reference values by including a healthy local control group in future research.

In **Chapter 6** we described the severity of PTC in the course of six months after the trauma and identified parameters known at first presentation after MTBI which can predict the severity of PTC. After six months, 22 of 79 patients (28%) reported more severe PTC compared with the pre-traumatic situation. Head-

ache, dizziness and/or nausea at the ER was found to be strongly associated with the severity of most PTC after six months. The prevalence of full recovery after six months increased from 50% in patients with three symptoms to 78% in those with no symptoms at the ER. Adding biochemical markers showed that all ten patients with no symptoms at the ER and normal markers made a full recovery. We conclude that identifying MTBI patients at the ER without headache, dizziness, nausea and normal serum marker concentrations may be a useful strategy for predicting good outcome.

In **Chapter 7** we evaluated the generic health status of MTBI patients in the course of six months after the trauma by means of the 36-item Short-Form Health Survey Questionnaire (SF-36). Improvements in the sub-scores of physical dimensions were statistically significant between two weeks and three months, while sub-scores of mental dimensions did not change much between these follow-up moments. In contrast, the improvement in the mental sub-score of 'Role-functioning emotional' was statistically significant between three and six months. Although the mean 'General health perception' did not change in the course of six months, all mean SF-36 sub-scores in patients with PTCs were significantly higher than in those without PTC (Mann Whitney U; $p < 0.0001$). We concluded that most MTBI patients have a normal generic health status after six months. However, patients with PTC after six months have a clearly impaired generic health status at that moment. In evaluating the outcome after MTBI, the SF-36 Health Survey Questionnaire seems a useful additional test to estimate the influence of MTBI on activities of daily life.

In **Chapter 8** we described the results of a clinical trial that evaluated the effect of six days of bed rest on the severity of PTC after MTBI. After adjustment for differences in baseline variables, we found that most PTC tended to be somewhat more severe in the bed rest group six months after the trauma. Two weeks after the trauma, most PTC in the bed rest group were slightly less severe than those in the no bed rest group, while the physical sub-scores on the SF-36 in the bed rest group were slightly better. None of these differences were statistically significant. Patients in the bed rest group reported significantly less severe dizziness during the intervention period.

Although the study had insufficient power to fully exclude any benefit of treatment, we concluded that it is very unlikely that six days of bed rest is an effective mean of speeding up recovery after MTBI. Bed rest may have some palliative effect within the first two weeks after the trauma.

In **conclusion**, mild traumatic brain injury is a common traumatic disorder in which signs of brain damage can be demonstrated from early elevated S-100B concentrations and possibly also from olfactory dysfunction. Although the overall outcome is good, about one-fifth of patients have post-traumatic complaints after six months. These complaints are associated with impaired generic health at the same time. The presence of headache, dizziness and/or nausea in the acute situation is predictive of post-traumatic complaints, while early elevated serum markers seem to have additional predictive value. Full bed rest after mild traumatic brain injury is not sufficient to improve the outcome after six months.

Future research in MTBI patients should thoroughly investigate the prediction and treatment of post-traumatic complaints after MTBI. Larger studies will be necessary to obtain precise estimates of combinations of parameters that predict which patients will recover completely. Such predictors should reduce needless follow-up, save money and prevent medicalisation of mainly young and healthy people.
In our opinion, larger studies evaluating the effect of bed rest are not useful. Alternative regular interventions such as 'complaints-driven' mobilisation and taking some time off work may be worth evaluating. Conversely, a strict and active mobilisation schedule or education about post-traumatic complaints could also be the subjects of future research.

CHAPTER 10

SAMENVATTING EN CONCLUSIES

Hoewel traumatische hersenletsels allerlei klachten en afwijkingen tot gevolg kunnen hebben en zelfs tot de dood kunnen leiden, betreft het meestal lichte traumatische hersenletsels (hersenschudding of commotio). De prognose van een dergelijk licht hersenletsel wordt in belangrijke mate bepaald door het optreden van post-traumatische klachten, zoals hoofdpijn, duizeligheid concentratie-problemen en depressiviteit. De frequentie en de ernst neemt gedurende de eerste drie maanden na het ongeval af, echter een deel van de patiënten heeft na zes maanden nog steeds klachten. Het voorkomen en voorspellen van deze klachten is belangrijk, omdat het optreden ervan tot hoge kosten voor de gezondheidszorg en verlies van arbeidsproductiviteit kan leiden.
Het is echter niet duidelijk of de post-traumatische klachten worden veroorzaakt door hersenbeschadiging of door factoren zoals de ongevalervaring, psychologie, emotionele factoren of motivatie.
Beschadiging van de hersenen bij patiënten met licht traumatisch hersenletsel kan worden aangetoond met behulp van afwijkingen op MRI-onderzoek van de hersenen en van markers in het bloed.

In dit proefschrift worden meerdere studies beschreven waarbij de gevolgen voor patiënten na een licht traumatisch hersenletsel (LTH) op de voorgrond staan. Het eerste gedeelte van het proefschrift bespreekt enkele algemene aspecten van het lichte traumatische hersenletsel. Allereerst wordt een overzicht gegeven over definities, diagnostiek en verschillende therapieën voor het LTH. Daarna is de incidentie berekend van hoofd en hersenletsel in een duidelijk omschreven verzorgingsgebied in Nederland. Verder werd een enquête uitgewerkt die de behandeling van LTH door Europese neurologen evalueert.
Het tweede deel van het proefschrift beschrijft de resultaten verkregen bij het vervolgen van patiënten met LTH vanaf het moment van het ongeval tot zes maanden daarna. De biochemische markers S-100B en Neuron Specific Enolase (NSE) zijn gemeten in bloed dat binnen zes uur was afgenomen bij deze patiënten. De gezondheidstoestand van de patiënten is geëvalueerd gedurende de eerste zes maanden na het ongeval.
Gedurende de eerste dagen na het ongeval hebben LTH patiënten vaak last van hoofdpijn nekpijn, misselijkheid, duizeligheid en braken. Tezamen met biochemische markers zou het aanwezig zijn van deze symptomen gebruikt kunnen worden bij het inschatten van de ernst van de hersenbeschadiging.

Mogelijk is de aanwezigheid van deze symptomen ook bruikbaar voor het voorspellen van de ernst van post-traumatische klachten.
Het is aangetoond dat poliklinische controle en voorlichting van LTH patiënten de ernst van de post-traumatische klachten op langere termijn kan verminderen. Om te beoordelen bij welke patiënten een dergelijke voorlichting noodzakelijk is, is de waarde van acute serum markers en symptomen voor het voorspellen van de ernst van post-traumatische klachten onderzocht.
Het effect van bedrust op post-traumtische klachten is nooit onderzocht. Hoewel aangetoond is dat bedrust de prognose van verschillende medische condities niet verbetert en soms zelfs verslechtert, schrijft in Nederland bijna de helft van 100 ondervraagde neurologen bedrust van een of meerdere dagen voor na een LTH. Om de waarde van bedrust na een LTH te beoordelen, hebben wij een gerandomiseerd onderzoek uitgevoerd waarbij het effect van geen bedrust versus het effect van zes dagen bedrust op de ernst van post-traumatische klachten na zes maanden is onderzocht.
Daarnaast hebben we ook de gevolgen van het LTH voor de algemene gezondheidstoestand van deze patiënten na twee weken, drie en zes maanden geëvalueerd. Deze gegevens zijn eveneens als uitkomst parameter in de bedrust trial gebruikt.

In **hoofdstuk 1** is een overzicht gegeven van de definities, differentiaaldiagnose en behandeling van LTH. We concludeerden dat traumatisch hersenletsel alleen als "licht" gedefinieerd mag worden als de score op Glasgow Coma Schaal (GCS) binnen 6 uur na het ongeval optimaal (EMV = 15) is. Een post-traumatische amnesie van minder dan 6 uur en/of bewusteloosheid van minder dan 15 minuten kunnen worden gebruikt als aanvullende diagnostische criteria. Deze bevindingen hebben wij toegepast bij onze definiëring van LTH in het verdere onderzoek.

In **hoofdstuk 2** is de incidentie van traumatisch schedel/ hersenletsel in het verzorgingsgebied van het academisch ziekenhuis Maastricht in 1997 berekend. Deze incidentie bedroeg 836 per 100.000 inwoners. De frequentie van ziekenhuisopnamen onder deze patiënten was erg laag (88/100.000) in vergelijking met andere landen. In 99% betrof het een relatief licht letsel (hoofdletsel en/of LTH) en in 75% een hoofdletsel zonder hersenletsel. Van de

patiënten met hersenletsel had 95% een LTH hetgeen overeenkomt met een incidentie van 201 LTH patiënten per 100.000 inwoners per jaar.

In **hoofdstuk 3** is onderzoek naar de behandeling van LTH patiënten in verschillende Europese ziekenhuizen verricht. Er werd een korte vragenlijst gestuurd naar neurologen in verschillende landen. Bijna alle responders (94%) hebben geantwoord dat zij patiënten met een LTH opnemen in het ziekenhuis voor een korte observatie. Eenenveertig neurologen adviseerden de patiënten om 1 tot 14 dagen bedrust te nemen. Door 64% werd geadviseerd het werk neer te leggen voor de duur van 1 tot 30 dagen. Door 70% van de neurologen werd tenminste een poliklinische controle na het ongeval noodzakelijk geacht. Het bestaan van landelijke richtlijnen voor de behandeling van LTH patiënten werd door minder dan de helft van de ondervraagden genoemd. Naar aanleiding van deze resultaten concluderen wij dat er geen consensus bestaat in Europese ziekenhuizen over de behandeling van LTH patiënten.

In **hoofdstuk 4** hebben we de serum concentraties van NSE and S-100B bij LTH patiënten met de concentraties van gezonde mensen vergeleken. De mediane NSE concentratie bij de patiënten was wat hoger (9,8 μg/l; 10 tot 90 percentiel 6,9 tot 14,3 μg/l) dan bij de gezonde patiënten (9,4 μg/l; 6,3 tot 13,3 μg/l). Mediane S-100B concentraties van patiënten waren significant hoger (0,25 μg/l; 0,00 – 0,68 μg/l) dan van controle personen (0,02 μg/l; 0,00 tot 0,13 μg/l). Er is bij LTH patiënten een relatie gevonden tussen verhoogde S-100B concentraties en het symptoom braken vlak na het ongeval. We concluderen dat S-100B mogelijk een marker is voor het aantonen van hersenbeschadiging bij LTH patiënten.

In **hoofdstuk 5** hebben we het voorkomen van kwantitatieve reukstoornissen na een LTH onderzocht. De relatie tussen de aanwezigheid van vroege LTH kenmerken (symptomen en serum markers) en de geurdrempel twee weken na het ongeval zijn ook bestudeerd. De prevalentie van een gestoorde reukzin bij LTH was twee weken na het ongeval 26%. Er werden geen relaties gevonden tussen vroege letselkenmerken en verhoogde geurdrempels. Deze bevinding is opmerkelijk, omdat de resultaten in hoofdstuk 6 aantonen dat andere vroege letselkenmerken wel associëren met uitkomstparameters na zes maanden. LTH

kan mogelijk leiden tot een gestoord reukvermogen. Bij vervolgonderzoek zal een controlegroep moeten worden onderzocht.

In **hoofdstuk 6** hebben we de ernst van post-traumatische klachten in het verloop van de eerste zes maanden na het ongeval onderzocht. Vervolgens hebben we parameters onderzocht die aansluitend aan het ongeval aanwezig waren, en mogelijk de ernst van post-traumatische klachten kunnen voorspellen. Zes maanden na het ongeval rapporteerden 22 van de 79 patiënten (28%) post-traumatische klachten. De aanwezigheid van hoofdpijn, duizeligheid en/of misselijkheid direct aansluitend aan het ongeval was sterk geassocieerd met de ernst van post-traumatische klachten na zes maanden. De kans op volledig herstel na zes maanden nam toe van 50% bij patiënten met drie symptomen tot 78% bij patiënten zonder symptomen direct na het ongeval. Alle patiënten met normale serum markers en zonder symptomen aansluitend aan het ongeval bleken na zes maanden volledig hersteld. We concluderen dat het identificeren van LTH patiënten zonder hoofdpijn, duizeligheid en misselijkheid op de eerste hulp een bruikbare strategie kan zijn bij het voorspellen van een goede prognose.

In **hoofdstuk 7** hebben we de algemene gezondheidstoestand van LTH patiënten gedurende de eerste zes maanden na het ongeval geëvalueerd met behulp van de SF-36 vragenlijst. De verbetering van de fysieke subscores op de SF-36 waren significant tussen twee weken en drie maanden terwijl de mentale subscores amper verbeterden in deze periode. Daartegen was de verbetering van de mentale subscore "functionering emotionele rol" significant tussen de derde en zesde maand. Hoewel de gezondheid in z'n algemeen gedurende de eerste zes maanden gemiddeld niet als verslechterd werd ervaren, waren alle SF-36 subscores slechter bij patiënten met post-traumatische symptomen na zes maanden. We concluderen dat de meeste patiënten zes maanden na een LTH een normale algemene gezondheidstoestand hebben, maar dat de algemene gezondheidstoestand bij patiënten met post-traumatische klachten aanzienlijk slechter is. De SF-36 vragenlijst lijkt een bruikbaar instrument bij het meten van de invloed van een LTH op het dagelijks leven van de patiënten in de eerste zes maanden na het ongeval.

In **hoofdstuk 8** werden de resultaten beschreven van een klinische trial waarbij LTH patiënten aansluitend aan het ongeval gerandomiseerd werd geadviseerd geen bedrust te nemen tegenover zes dagen volledige bedrust. We vonden dat post-traumatische klachten na zes maanden, in de groep die bedrust kreeg geadviseerd, ernstiger leken dan in de groep die dit advies niet kreeg. Twee weken na het ongeval leken de post-traumatische klachten in de bedrust groep wat minder te zijn. Beide verschillen waren niet significant. Patiënten in de bedrust groep rapporteerden minder duizeligheid tijdens de interventie.
Hoewel deze studie statistisch niet genoeg "power" had om een gering voordeel van de bedrust interventie uit te sluiten, concluderen wij dat het heel onwaarschijnlijk is dat zes dagen bedrust na een LTH het herstel na zes maanden in positieve zin beïnvloedt. Mogelijk heeft bedrust een tijdelijk positief effect tijdens de eerste twee weken na het ongeval.

Samenvattend is LTH een veel voorkomende aandoening, waarbij hersenbeschadiging aangetoond kan worden met behulp van vroeg verhoogde S-100B concentraties in serum. Ook een post-traumatische reukstoornis zou hiermee in verband kunnen worden gebracht.
Hoewel de prognose over het algemeen goed is, heeft ongeveer een kwart van de patiënten met een LTH na zes maanden nog post-traumatische klachten. Deze klachten zijn geassocieerd met een slechtere algemene gezondheidstoestand op dat moment.
De aanwezigheid van hoofdpijn, duizeligheid en/of misselijkheid direct na het ongeval is voorspellend voor de ernst van post-traumatische klachten waarbij serum markers mogelijk nog een aanvullende waarde kunnen hebben.
Volledige bedrust direct na het ongeval is niet zinvol ter verbetering van de prognose van een LTH.

Toekomstig onderzoek bij patiënten met LTH is nodig voor het voorspellen en behandelen van post-traumatische klachten na een LTH. Grotere studies zijn nodig om de juiste combinaties van voorspellende parameters voor het wel of niet ontstaan van post-traumatische klachten te bepalen. Dergelijke voorspellende parameters kunnen overbodige follow-up na een LTH beperken, medicalisering van jonge gezonde mensen voorkomen en tevens geld besparen.

Nieuwe studies naar het effect van bedrust op post-traumatische klachten lijken overbodig. Het nut van andere gebruikelijke interventies zoals "klacht-gerelateerde" mobilisatie en onderbreking van het werk verdient verder onderzoek. Daarnaast zou ook het effect van minder gebruikelijke interventies zoals een strikt en actief mobilisatieschema of het geven van voorlichting over mogelijke post-traumatische klachten onderwerp van onderzoek kunnen zijn.

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DANKWOORD

Naast de anonieme patiënten die meededen aan dit onderzoek wil ik verschillende mensen in mijn omgeving bij naam noemen en bedanken voor hun steun gedurende de jaren waarin dit proefschrift tot stand kwam.

Geachte Professor Troost, beste Jaap. Vanuit de collegebanken kreeg ik de gelegenheid de basis voor dit proefschrift te leggen. Vrijwel direct aansluitend begon ook mijn klinische opleiding. Beide sporen heb ik zo goed mogelijk geprobeerd te combineren. Soms gaf mij dat het gevoel van een onmogelijke spagaat, maar jouw vertrouwen in een goede afloop heeft aangetoond dat zelfs een tweesporen beleid tot resultaten kan leiden.
Dr. A Twijnstra, beste Albert, als student gaf je me al de gelegenheid om te proeven aan de wetenschap. Je stimuleerde me om in andere keukens te kijken, maar legde uiteindelijk de basis voor het recept van dit Maastrichtse proefschrift. Bedankt voor je begeleiding en stimulans gedurende het gehele onderzoekstraject. Je rol als copromotor in het laatste jaar van mijn opleiding is de kroon op onze wetenschappelijke en klinische samenwerking.
Drs. Ir. P. Leffers, beste Pieter, als epidemioloog heeft je begeleiding zich niet beperkt tot het bewaken van de methodologie alleen. Achter de schermen, maar ook tijdens het overleg, was je inbreng essentieel. Sinds afgelopen jaar associeer ik Koninginnedag niet meer met koekhappen op een drukke Amsterdamse rommelmarkt maar met mooie lineaire regressies in een rustige Maastrichtse stadstuin. Je afwezigheid op "het podium" ervaar ik als een gemis.
Dr. P. Menheere, beste Paul, bij de opzet van het onderzoek was er slechts een pilot-plaats voor het klinisch chemisch onderzoek. Uiteindelijk was je bijdrage echter zo belangrijk dat er, voorafgaande aan de promotie, een minisymposium aan gewijd kan worden. Bedankt voor de samenwerking.
Drs. S. Meerhoff en Drs. J. Rutten, Saskia en Joost, als student-assistenten waren jullie onmisbaar; als fijne collega-onderzoekers trouwens ook. Saskia, jij legde de letterlijke (data)basis voor het onderzoek en bent als paranimf nauw betrokken bij de finale. Joost, jij was de onzichtbare logistieke motor tijdens de follow-up.

Bedankt, en hoewel jullie je eigen weg alweer vervolgd hebben, zullen onze paden ongetwijfeld weer kruisen.
Drs. S. Stapert, beste Sven, samen hoopten we op meer patiënten voor onze onderzoekslijnen. Bedankt voor je vasthoudend meedenken en succes met de afronding van je eigen promotieonderzoek.
Neurologen en collega (oud)assistenten, hoewel ik me wel eens mopperend uitliet over de achterblijvende inclusiecijfers, is het uiteindelijk mede aan jullie te danken dat ik de data voor dit proefschrift heb kunnen verzamelen en bewerken. Velen van jullie beschouw ik intussen als vrienden waarmee ik hopelijk nog mooie dingen in het verschiet heb, zowel tijdens als naast het werk.
Peter, net zoals ik nog steeds niet weet of je me af en toe liet winnen met schaken, weet ik ook niet of ik je als paranimf beloon of juist straf. In ieder geval alvast bedankt voor je back-up.
Alle medewerkers van de afdeling spoedeisende hulp, polikliniek neurologie en secretariaat neurologie in ons ziekenhuis, bedankt voor jullie hulp en medewerking aan het onderzoek.
Marjolein en Marjon, bedankt voor de lage inloopdrempel. In de rol van deskundige en vertrouwde buren toetsten jullie als eerste buitenstaanders het concept van dit boekje.
Vrienden van Plutarchus, het afronden van dit proefschrift is een gebeurtenis die mede gebaseerd is op inspiratie die wij door de jaren heen deelden en altijd zullen delen.
Lieve pap en mam, bedankt voor het warme nest, het vertrouwen en de stimulans, toen en nu. Jullie hebben me geleerd dat de lat soms iets hoger kan zonder daarbij mijn nek te breken. Peter, Simone en Daan, alweer vijftien jaar geleden verdwaalde ik in de Limburgse heuvels en bleef er zelfs hangen. Voorlopig verzuim ik mijn taak als oudste broer; bedankt dat jullie aan de Hollandse kust een oogje in het zeil hielden.
Eva, je bent mijn kleine ster; jouw vrolijkheid en aanpassingsvermogen kregen we cadeau en geven me het vertrouwen dat je broertje of zusje ons leven nu nog mooier kleurt.

Bedankt liefste Annick, met jou samen is geen zee te hoog. Jij moest in de rol van partner, collega en moeder vaak alle zeilen bijzetten maar was altijd naast me. Ik verheug me op alles wat nog voor onze boeg ligt.